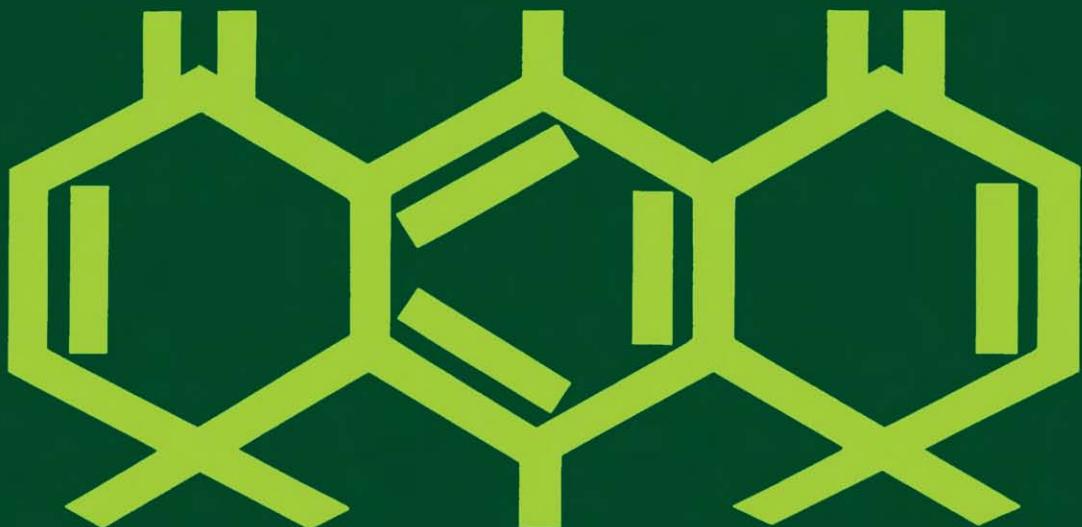


*A Manual of*  
**Adverse  
Drug  
Interactions**

Fifth Edition

**J.P. GRIFFIN  
P.F. D'ARCY**



**Elsevier**

A MANUAL OF  
ADVERSE DRUG  
INTERACTIONS

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# A MANUAL OF ADVERSE DRUG INTERACTIONS

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# **FOREWORD**

For twenty years this book, now in its Fifth edition, has provided information on adverse drug interactions that is unrivalled in coverage and scholarship. Adverse drug reactions, many of them ascribable to interactions with other drugs or with chemical substances in food or the environment, are thought to cause or complicate one in twenty of hospital admissions and are thus responsible for much human misery and cost. They pose a problem worldwide even in those countries with the most careful and vigilant regulatory authorities and are an important — if often overlooked — cause of preventable morbidity and mortality. Paradoxically, awareness of adverse drug reactions and interactions amongst doctors is heightened in those countries with more conservative prescribing habits as opposed to those with a more liberal approach to polypharmacy and extensive drug use.

Better monitoring, especially at local level, has identified many of these adverse reactions and pharmacoepidemiology is a well established discipline in medical science. Systematic surveys and reviews and study of linkage data together with fundamental pharmacogenetics yield ever more accurate predictive indices for reducing hazard.

If safety in drug use is to improve, education of prescribers is vitally important. This book with its up-to-date and coordinated approach, serves that purpose well. The real threat, as the authors remind us, is the ignorance of practitioners not drug interaction itself, for most adverse effects can be reversed speedily if recognized.

Professor Dame ROSALINDE HURLEY  
DBE, LLB, MD, D Univ, FRCPath, FRCOG, FFPM  
Barrister, Inner Temple

## PREFACE TO FIFTH EDITION

The objective of this book was stated in the preface to the 1st Edition, to present in a readily accessible and understandable form the major drug interactions that are likely to be encountered in practical therapeutics. This still remains the aim of the 5th Edition.

Between the publication of the 4th Edition and the preparation of the 5th Edition there have been very significant changes in the treatment of a number of conditions. For example, for nearly 25 years prior to the last edition there had been only the introduction of one new antiepileptic agent, sodium valproate, but since the last edition some eight new agents have been introduced into the therapeutic armamentarium. This is not an isolated example. We have therefore taken the opportunity to rewrite completely and to reformat the book to the extent that it is almost a totally new work.

Just before the 1st Edition was published in 1975, a *Lancet* Editorial (19th April 1975) said that "the publication of huge lists and tables will induce in doctors a drug-interaction anxiety syndrome and lead to therapeutic paralysis". We were persuaded to expect better things of our colleagues and envisaged that few would turn into "paralysed medical ostriches" as a result of this or any other book. We believed that a better awareness of possible hazards of medication and possible interactions between drugs by those who use them — doctors, pharmacists and patients — can only result in safer and more effective therapeutics. We have, however, been concerned by the development of "Therapeutic Conservatism" in which doctors have been shown to be reluctant to prescribe newer and often more effective, safer and more pharmaco-economically efficient medicines. This has been due to the Government's downward pressure on medicines' expenditure rather than concerns for the safety of these more recently introduced treatments.

We have been concerned that paracetamol has been licensed with a built-in antidote, methionine. It is undesirable that patients taking paracetamol should be exposed to high doses of a substance for which for the most part they have no need, and which is itself not free of risk. Methionine has been shown to interact with a variety of substances including oral contraceptives and to destabilize controlled diabetics. As a general principle such blanket preventative measures are to be deprecated. The withdrawal of a paracetamol/methionine combination by one major manufacturer is to be applauded. The real issue of whether it should have been approved for marketing in the first place is a mute point.

J. P. GRIFFIN  
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P. F. D'ARCY  
Lisburn  
Co. Antrim

## **PREFACE TO FOURTH EDITION**

In the preparation of this edition we are pleased to welcome Dr Chris Speirs as a co-author.

It is becoming very clear that the literature in the field of interactions is also requiring some judgemental element to be exercised as to its clinical significance when therapeutic judgements are being made. We have attempted to do this by indicating by the boldness of typeface the relative importance that should be given to various reports. We are also aware that there are drawbacks to this approach since, rarely, for some unfortunate individuals a reaction may have unexpected severity; for them such interactions are therefore very significant. It is because of this awareness that we have not excluded reference to some usually clinically unimportant interactions.

Finally, we would wish to reiterate the warnings we gave in the preface to the Third Edition regarding the increasing level of medicolegal litigation and have therefore taken the step of reproducing the Preface to the Third Edition.

J. P. GRIFFIN  
Digswell  
Herts

P. F. D'ARCY  
Holywood  
Co. Down

C. J. SPEIRS  
Fetcham  
Surrey

## PREFACE TO THIRD EDITION

At the time of completion of this third edition the Medical Defence Union's Annual Report for 1982 was available and to us, as authors of a book on drug interactions, it made interesting reading.

One case settled for £44 000 was due to phenylbutazone-induced potentiation of warfarin, which was followed by an intraspinal haemorrhage resulting in an incomplete tetraplegia at the level of C7.

A second case was of a 64-year-old man with a history of cervical spondylosis, hypertension and previous myocardial infarction who attended his general practitioner complaining of pain and numbness in his left wrist and fingers. The doctor diagnosed tenosynovitis and prescribed phenylbutazone. Ten days later the patient was admitted to hospital with severe neurological abnormalities. These were subsequently shown to be due to haemorrhage into the spinal cord. The patient had been on long-term anticoagulants and the phenylbutazone had potentiated their effect. The notes held by the general practitioner had the words 'on anticoagulants' written on the folder but when a new folder had been used, this information had not been transferred to it. This case was also settled for £44 000.

One suspects that in the future as patients become more litigation conscious, more claims for drug-induced injury due to drug interaction will be initiated. In the Medical Defence Union's Annual Report for 1982 they discuss this current trend in increased litigation and ask why more claims? Why are damages much higher? The answer is that litigation is easier with increased opportunities to gain legal aid, wages are higher and reimbursement for lost earnings is also higher.

It is interesting that in the first case the solicitor's letter stated that 'Butazolidin is a well known potentiator of coumarin anticoagulants of which warfarin is one' . . . 'the prescribing of Butazolidin for a patient known to be taking warfarin routinely was a breach of your professional duty to him'.

It is clear from the tone of these and other recent cases that ignorance of drug interactions is likely to result in high financial reimbursement to those that suffer injury. When doctors are prescribing their principle should be 'do not use two if one will do'.

J. P. GRIFFIN  
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Holywood  
Co. Down

## PREFACE TO FIRST EDITION

The object of this book is to present in a readily accessible and easily understandable form the major drug interactions that are likely to be encountered in practical therapeutics, and to draw attention to some theoretical interactions that could be serious or life threatening. The book is intended as a convenient desk reference book for the prescribing physician and the pharmacist.

A *Lancet* Editorial (19 April 1975) said that 'publication of huge lists and tables will induce in doctors a drug-interaction-anxiety syndrome and lead to therapeutic paralysis'. We are persuaded better things of our colleagues and envisage few will turn into paralysed medical ostriches as a result of this or any other book on the potential hazards of drug therapy. We believe that awareness of possible hazards of medication and possible interactions between drugs on the part of those who use them, both doctors and pharmacists, can only result in better therapeutics with benefit to the patient in terms of both safety and efficacy.

J. P. GRIFFIN  
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Herts

P. F. D'ARCY  
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Co. Down

## **ACKNOWLEDGEMENTS**

We are grateful to all those who have assisted us in any way in the production of any of the editions of this book. New editions, to a greater or lesser extent, are built on the experience gained in the production of earlier editions. In the 4th Edition we made a comprehensive acknowledgement to all those who assisted in any way. The 5th Edition has been a total rewrite and we are therefore only going to acknowledge here those who have made a specific contribution to this edition.

During the past few years one or other of us have published extensive articles in Adverse Drug Reactions and Toxicological Reviews. These papers have formed the basis of Chapters 4.2, 4.4, 13 and 15. We wish to thank Oxford University Press for permission to use extensively material that appeared in the following articles:

- D'Arcy PF and Griffin JP (1995) Interactions with drugs used in the treatment of depressive illness. *Adverse Drug React Toxicol Rev* **14**, 211–231.
- D'Arcy PF (1995) Nutrient drug interactions. *Adverse Drug React Toxicol Rev* **14**, 233–254.
- D'Arcy PF (1996) Drug interactions with medicinal plastics. *Adverse Drug React Toxicol Rev* **15**, 207–219.
- Griffin JP (1996) Drug interactions with agents used in the treatment of epilepsy. *Adverse Drug React Toxicol Rev* **15**, 221–246.

We would therefore like to thank the publishers and the typesetter for their skills and assistance, the Library staff at the Royal Society of Medicine and the staff of the Medical Library of The Queen's University of Belfast, colleagues who have assisted in providing advice in the preparation of certain changes, namely Professor Alan Richens of Cardiff and Dr Rashmi Shah of the Medicines Control Agency. We would also thank Mrs Elspeth Gladwin for expert secretarial assistance. Above all we are indebted to our respective wives for their long sufferings while this and previous editions have consumed much of our time.

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# **PART 1**

## **Commentary on Drug Interactions and Their Mechanisms**

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# INTRODUCTION: A WIDENING PROBLEM

Over 20 years ago, an editorial on drug interactions in the *Lancet* (19 April 1975) said that the “publication of huge lists and tables will induce in doctors a drug-interaction-anxiety syndrome and lead to therapeutic paralysis”. This prediction has not come about, although the problem of drug interactions is still with us and the spectrum is widening as new drugs are introduced. Indeed it could be said that the nature of the problem has also widened for in the intervening years drug interactions have come to embrace interactions with food and with herbal medicines as well as the more numerous and better recognized drug-drug interactions.

There is little doubt that drug-drug interactions can often be serious, even life-threatening. They can also be very expensive, and evidence from the Medical Defence Unions’ Reports of over 10 years ago reveals that one case which settled for £44 000 was due to phenylbutazone-induced potentiation of warfarin which was followed by an intraspinal haemorrhage resulting in an incomplete tetraplegia at the level of C7. It is interesting in this case that the solicitor’s letter stated that “Butazolidin is a well known potentiator of coumarin anticoagulants of which warfarin is one” . . . “the prescribing of Butazolidin for a patient known to be taking warfarin routinely was a breach of your professional duty to him”.

Knowledge of the ‘state of the art’ has much advanced since the 1980s and what were then novel and scientifically interesting interactions are now established and well-recorded interactions in standard books of reference. Knowledge has advanced but there has been little progress in the way in which it is generated.

## SOURCES OF INFORMATION

Most reports of drug-drug- or drug-food interaction arise primarily from experience in the clinic. Some of these are anecdotal and may not be reported again, whilst others represent the first warning signs of a wider cohort of cases that is yet to be realised. Their purpose is to report the interaction and explain its hazard so that others can avoid it occurring; however, few of these reports are able to indicate the precise mechanism of the interaction.

Generally, animal experiments have not contributed much of substance to knowledge about interactions. Admittedly, the early work of Conney and his associates (1956, 1957) in rats did much to explore the nature and organization of enzyme systems in liver microsomes, but it was the human studies of Levy (1970) and Neuvonen *et al.*, (1970) that provided the now classical evidence that the salts of divalent or trivalent metals formed non-absorbable complexes with tetracyclines and reduced their absorption, resulting in sub-therapeutic levels in the plasma. It

was observation in patients that gave the first indication that concomitant medication could antagonize the efficacy of oral contraceptives (Dossetor, 1975). It was in tuberculosis patients that the apparent interaction between PAS and rifampicin was first recognized and later to be explained that the interaction was not due to PAS but to the bentonite content of its granules (Boman *et al.*, 1971). One of us (PFD'A) was reminded of this latter interaction in recent months when a lady in Belfast who had been a TB patient at that time and had been receiving rifampicin and PAS, mentioned that without warning or explanation her treatment had been changed to rifampicin plus isoniazid.

One of the advantages of the attention that has been focused on adverse drug interactions over the past 20 years or so is that many drug-drug and drug-food interactions are now predictable and many of the unwanted consequences of using drug combinations can be avoided by simply adjusting the dosage of one or more of the interactants. As a result of this, there has been a considerable improvement in the safety and efficacy of therapy with drug combinations.

However, the focus on drug interactions has always been more on their hazards than their advantages. This is the correct orientation since the vast majority of interactions are hazardous. An awareness of the possible hazards of medication and possible interactions between drugs on the part of those who use them, doctors and other health professionals, can only result in better therapy with benefit to the patient in terms of both safety and efficacy. Many excellent publications have explored the nature of drug interactions and their message has filtered down to the patient level being expressed by the maxim 'do not use two drugs when one will do'.

## THE LITERATURE ON DRUG INTERACTIONS

The literature on drug interactions tends to be very non-specific and in the last 20 years or so it has become voluminous and has been cluttered up with a sticky mass of largely irrelevant studies of interactions in animal models and in single-dose pharmacokinetic studies in animals and in young adult age groups of volunteers. Such studies can be of predictive value, but only if they mimic the clinical situation and if they relate to drug combinations and dosage regimens that are normally used in sick patients.

It is clear that the literature requires some judgmental element to be exercised as to its clinical significance. It is the single reports in the correspondence columns of medical and pharmaceutical journals that, although often anecdotal and uncorroborated, have, in our view, made a major contribution to elucidating the nature and extent of interactions. Such reports are also useful since they often stimulate other clinicians to report similar experiences in their own patients.

There is still need to focus attention on those drug-drug or drug-nutrient interactions that really do influence the safety of efficacy of human drug therapy in all age groups. If mechanisms of interaction are clearly understood then it may be possible to develop animal/biochemical/tissue culture/physico-chemical or other types of

models of interactions to which new molecules could be exposed during their development stages. It is hardly satisfactory or safe to have to rely on patients experiencing adverse interactions before they can be established and documented. It is hoped that by discussing mechanisms of interactions, this volume will stimulate interest in investigating the possibility and potential of developing meaningful models.

Whereas over the years books, our own included, have classified and detailed drug-drug interactions into their respective categories (Fig. 1), they have not been so expressive about the individual mechanisms that underlie these interactions. Their prime objective was to inform about the interaction and its clinical management.

In our preliminary thoughts and discussions in the planning of this book, we decided to forego mention of theoretical interactions with minor and relatively unimportant drugs and attempt to produce a volume that dealt specifically with those drugs that have major clinical use in the United Kingdom. The number of these is not as great as one might think. There are in fact a total of just 50 drugs that come into this category (*Tables 1a, 1b*). We have therefore concentrated our attention on drugs that are actually taken by patients and their interactions with other medication or foodstuffs.

In recent years there has been intensive research into the mechanisms of established drug-drug interactions in man. We have therefore decided to give details

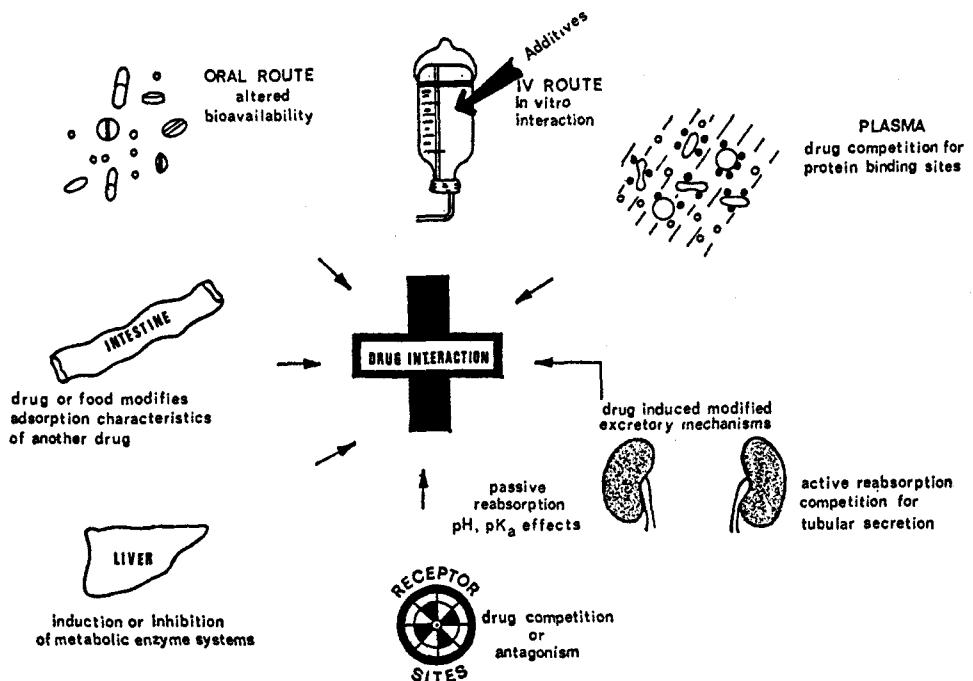


Fig. 1. Sites of drug-drug and drug-food interactions.

## 6 A MANUAL OF ADVERSE DRUG INTERACTIONS

**Table 1a.** TOP 50 ACTIVE INGREDIENTS BY INN NAME PRESENTED IN RANK ORDER BY NUMBER OF UK PRESCRIPTIONS IN 1994\*

1. Salbutamol	26. Cimetidine
2. Beclomethasone	27. <i>Plantago ovata</i>
3. Amoxycillin	28. Diazepam
4. Acetylsalicylic acid	29. Betamethasone
5. Atenolol	30. Enalapril
6. Nifedipine	31. Propranolol
7. Paracetamol	32. Terfenadine
8. Ibuprofen	33. Chloramphenicol
9. Bendroflumethiazide	34. Trimethoprim
10. Temazepam	35. Amitriptyline
11. Levothyroxine	36. Clotrimazole
12. Diclofenac	37. Nitrazepam
13. Ranitidine	38. Naproxen
14. Frusemide (furosemide)	39. Ferrous iron
15. Lactulose	40. Budesonide
16. Prednisolone	41. Captopril
17. Digoxin	42. Cromoglycate
18. Isosorbide mononitrate	43. Warfarin
19. Penicillin V	44. Diltiazem
20. Erythromycin	45. Quinine
21. Nitroglycerin	46. Lisinopril
22. Omeprazole	47. Terbutaline
23. Dothiepin	48. Flucloxacillin
24. Hydrocortisone	49. Carbamazepine
25. Influenza vaccine	50. Oxytetracycline

\*Source: Griffin (1995).

**Table 1b.** TOP 50 ACTIVE INGREDIENTS BY INN NAME PRESENTED IN RANK ORDER BY NUMBER OF UK PATIENTS EXPOSED IN 1994\*

1. Amoxycillin	26. Cefalexin
2. Salbutamol	27. Naproxen
3. Beclomethasone	28. Cromoglycate
4. Ibuprofen	29. Nifedipine
5. Influenza vaccine	30. Nitroglycerin
6. Penicillin V	31. Cimetidine
7. Erythromycin	32. Prochlorperazine
8. Paracetamol	33. Hepatitis A vaccine (inactivated virus)
9. Chloramphenicol	34. <i>Plantago ovata</i>
10. Trimethoprim	35. Pseudoephedrine
11. Hydrocortisone	36. Frusemide (furosemide)
12. Diclofenac	37. Omeprazole
13. Clotrimazole	38. Fusidic acid
14. Terfenadine	39. Doxycycline
15. Flucloxacillin	40. Typhoid vaccine
16. Betamethasone	41. Ferrous iron
17. Acetylsalicylic acid	42. Levothyroxine
18. Prednisolone	43. Dothiepin
19. Bendroflumethiazide	44. Diazepam
20. Tetanus vaccine	45. Metronidazole
21. Atenolol	46. Terbutaline
22. Lactulose	47. Propranolol
23. Oxytetracycline	48. Budesonide
24. Ranitidine	49. Paraffin oil
25. Temazepam	50. Norethisterone

\*Source: Griffin (1995).

about mechanisms of interaction in Part 1 of this book. Of necessity this has had to be brief, a more detailed account of mechanisms of drug interactions has been given in a recent and companion volume (D'Arcy *et al.*, 1996). It is convenient within this context to classify these introductory discussions on mechanisms into two major parts: firstly, those involved in pharmacokinetic drug interactions and secondly, those involved in pharmacodynamic drug interactions.

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## **A. Pharmacokinetic drug Interactions**

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# **1. DRUG-DRUG AND NUTRIENT-DRUG INTERACTIONS AT THE ABSORPTION SITE**

There are many facets of drug-drug interactions at the absorption site. For the majority of drugs this is the stomach and small intestine. The influence of wide-ranging factors, such as the effect of fluid volume of gastrointestinal physiology, splanchnic blood flow, passive diffusion, gastric emptying time, pH of the intestinal contents, intestinal motility, ionic content of foods, dietary fat, and gastrointestinal disease can have considerable effect on the absorption of drugs and they are mechanisms common to both drug-drug and drug-food interactions in the gut. An excellent review on drug interactions in the gastrointestinal tract has recently been published by Lipka *et al.* (1996) and this, together with a companion review on drug-food interactions affecting drug absorption by Welling (1996), presents a synopsis of current knowledge in this field.

The two topics of drug-food interactions affecting drug absorption and the effect of drugs on food and nutrient absorption are closely related but quite distinct. In this present volume only the former topic is addressed. No attempt has been made to discuss the latter topic; material on this latter topic has been reviewed elsewhere (Basu, 1988; Roe, 1989; Trovato *et al.*, 1991; D'Arcy, 1995).

It is only in relatively recent years that studies on food-drug interactions have been actively pursued. This work was heralded by the major review of Welling (1977). It is surprising that the study of drug-food interactions should have lagged behind that of drug-drug interactions. It is noticeable that food-drug interactions are not as often reported as drug-drug interactions although their potential frequency is far greater since food is by far the most common substance associated with the ingestion of oral doses of medicine. In our experience, medical and pharmacy practitioners are not well informed about food-drug interactions and therefore may fail to pass on cautionary advice to their patients.

Perhaps one of the most troublesome and well reported of food-drug interactions was the interaction between tyramine-containing foods and MAOI-antidepressants during the early 1960s (see reviews by D'Arcy, 1979; Brown *et al.*, 1989; Lippman and Nash, 1990). Deaths from eating cheese whilst taking MAOIs was given great publicity and this type of interaction did much to create an awareness of the potential of foods to interact with medicines.

Monoamine oxidase type A preferentially oxidatively de-aminates adrenaline, noradrenaline and serotonin, while type B preferentially metabolizes benzylamine and phenylethylamine. Dopamine and tyramine are de-aminated by both forms of

the enzyme. The traditional monoamine oxidase inhibitors, such as phenelzine and tranylcypromine inhibit both types A and B of the enzyme. Selective MAOI inhibitors, like brofaromine, moclobemide and clorgyline have been introduced with a selective and reversible inhibition of monoamine oxidase (type A), and selegiline, which reversibly inhibits type B, is an adjunct in the treatment of parkinsonism. The dietary restrictions that need to be observed with the traditional MAOIs (type A and B) are much less stringent with the new selective inhibitors.

It was largely the interactions with food that led to a virtual replacement of the use of MAOI antidepressants by the tri- and polycyclic antidepressants. That this may have been a collective error of judgement is now being realized; perhaps the MAOIs are not so bad after all!

The effect of heavy metal ions in milk and other dairy products on the absorption of tetracyclines was another milestone which raised the sensibility of clinicians to the dangers of food-drug interactions (Braybrooks *et al.*, 1975; Chin and Lach, 1975; Neuvonen *et al.*, 1970).

It took almost 20 years of tetracycline usage before the milk-tetracycline interaction was fully recognized. Once this interaction was realized, it was only a relatively short time before the spectrum of such interactions was widened and it was realized that it was not uncommon that the absorption from the gut of other antimicrobial agents, or reduction of their bioavailability, could be seriously influenced by food or metal ions.

Even more recent work has shown that the bisphosphonates, used to treat a broad range of bone disorders, including osteolytic bone metastases, hyperparathyroidism, Pagets disease of bone and established vertebral osteoporosis in women, can be completely antagonized by food and vitamin-mineral supplements with a high calcium content (Fogelman *et al.*, 1984, 1985, 1986; Fels *et al.*, 1989; Compston, 1994). Much of the study of bisphosphonates on bones have been reviewed in the comprehensive book edited by Bijvoet *et al.* (1995).

## **2. DRUG INTERACTIONS AT PLASMA AND TISSUE BINDING SITES**

The importance of plasma protein-binding displacement as a clinically important drug interaction mechanism is controversial. When a displacing agent interacts with a primary drug the result is an increase in the free concentration of the displaced drug in the plasma. In the past, it has been wrongly assumed that these free drug concentrations will remain raised. This is not so. What in fact occurs is that the increased free drug in the plasma quickly distributes throughout the body and may localize in the tissues. When equilibrium is again reached (assuming the volume into which the drug distributes is large) the free concentration in the plasma will be the same, or near to its pre-interaction level. The 'total' drug concentration (i.e. bound plus free drug) in the plasma will decrease after the equilibrium for free drug is reached. The ultimate consequence, therefore, of a plasma protein-binding displacement interaction is to lower total drug concentration in the plasma and to leave free drug concentration unchanged. Since pharmacological actions, including toxicities, correlate with free drug in the plasma, any increased effect seen after displacement is usually of a transient nature and, in most cases, is clinically unimportant.

### **PROTEINS INVOLVED IN DRUG BINDING**

The main binding proteins in plasma are albumin and  $\alpha_1$ -acid glycoprotein. Albumin consists of a single polypeptid chain and is present in plasma at a concentration of 35–45 g/l (ca. 0.6 mM) in normal healthy subjects. The binding of albumin can be compromised by the presence of increased concentrations of endogenous displacing agents, e.g. in kidney disease. Albumin, unlike  $\alpha_1$ -acid glycoprotein which only binds basic drugs, can bind both acidic and basic compounds. Diseases and events that can increase the concentration of  $\alpha_1$ -acid glycoprotein will therefore result in increased drug binding, e.g. myocardial infarction and Crohn's disease (Piafsky *et al.*, 1978).

Disease states can alter plasma protein binding and these can complicate drug-drug binding interactions. A number of authors have investigated these phenomena and their work has been summarized in tabular form by McElnay (1996). His table is summarized here (*Table 2*).

As well as protein concentration, the other main determinant of the amount of protein binding to plasma is the number of binding sites per molecule of protein and the strength of binding between the drug and its binding site. Two major binding areas have been identified on albumin, e.g. piroxicam has been shown to

Table 2. THE INFLUENCE OF DISEASES ON DRUG PLASMA PROTEIN BINDING\*

Drug	Disease	% free or free fraction (control vs. patient)	Sig. diff.	Clinical sig./ comment	References
Carbamazepine	Alc. liver disease, renal failure, rheumatoid arthritis, ulcerative colitis	22.7 vs. 19.5	Y	Not clinically sig. Caution in interpreting total drug concentrations. Correlation with AGP shown.	Barruzzi <i>et al.</i> , 1986
Diazepam	Early pregnancy	1.8 vs. 1.9	N	Large $V_d$ and therapeutic index means change is not clinically important in chronic use. If used in status epilepticus may have potentiated action in late pregnancy due to increased free fraction.	Perucca <i>et al.</i> , 1981
	Mid pregnancy	1.8 vs. 2.1	Y		
	Late pregnancy	1.8 vs. 2.6	Y		
	Uraemia	2.9 vs. 4.5	—	Not indicated. Site II not affected by carbamylation. Endogenous binding inhibitors implicated.	Calvo <i>et al.</i> , 1982
	Uraemia	1.64 vs. 3.23	Y	Not indicated, but an important difference implicated when interpreting kinetic data with regard to type of renal disease and the protein involved in binding.	Grossman <i>et al.</i> , 1982
	Kidney transpl.	1.50 vs. 2.11	Y		
	Nephrotic syndr.	1.60 vs. 3.55	Y		
	Chronic cardiac failure	≈1 vs. 1.5	N	Does not alter diazepam binding site affinity.	Fitchl <i>et al.</i> , 1983
	Acute uraemia	2 vs. 6	Y	Large therapeutic index means that drug effect can be monitored clinically as clinical end point can be determined safely.	Tiula and Neuvonen, 1986
	Chronic uraemia	2 vs. 4	Y		
	Age-related decrease in renal function	1.8 vs. 3.0	Y	Pharmacokinetic changes but no clinical implication.	Tiula and Elfving, 1987
	Chronic cardiac failure	6 vs. 5.9	N	Not significant.	Fitchl <i>et al.</i> , 1983
Digitoxin	End-stage renal disease (haemodialysis)	2.0 vs. 2.5	N	Difference too small to have any therapeutic consequence.	Lohman and Merkus, 1987
Disopyramide	MI	0.25 vs. 0.15 (at 2 mg/l) 0.53 vs. 0.32 (at 5 mg/l)	Y	Binding varies with drug and protein conc. May be clinically significant as AGP conc. decreases post MI.	David <i>et al.</i> , 1983

Table 2. CONTINUED

<i>Drug</i>	<i>Disease</i>	<i>% free or free fraction (control vs. patient)</i>	<i>Sig. diff.</i>	<i>Clinical sig./ comment</i>	<i>References</i>
	MI	0.2 vs. 0.13	Y	Not indicated. Pharmacokinetic change suggested. Interpretation of total drug levels caution.	Caplin <i>et al.</i> , 1985
Flecainide	MI	39 vs. 47	Y	Not indicated. Endogenous compounds may lead to displacement and decreased binding.	Caplin <i>et al.</i> , 1985
Imipramine	Chronic cardiac failure	19 vs. 18	N	Drug binding not affected.	Fitchl <i>et al.</i> , 1983
Lignocaine	Uraemia Kidney transpl.	30.7 vs. 20.8 33.7 vs. 24.6	Y Y	Interpreting kinetic data with regard to the type of renal disease and the protein involved in binding may be important.	Grossman <i>et al.</i> , 1982
	Nephrotic syndr.	30.4 vs. 34.2	N		
	NIDDM	32 vs. 30	N	Not indicated (but no change expected).	O'Byrne <i>et al.</i> , 1988
Lorcainide	Cardiac arrhythmia	26.03 vs. 24.70	N	Not significant.	Somani <i>et al.</i> , 1984
	Renal disease	26.03 vs. 29.04	N	Not significant.	
Metoclopramide	Renal disease	0.6 vs. 0.59	N	Not significant.	Webb <i>et al.</i> , 1986
Phenylbutazone	Alc. hepatitis Alc. cirrhosis	6 vs. 13 6 vs. 19	Y Y	Not known. Bilirubin and hypoalbuminaemia implicated in binding defect.	Brodie and Boobis, 1978
Phenytoin	Early pregnancy** Mid pregnancy Late pregnancy	9.7 vs. 10.6 9.7 vs. 10.9 9.7 vs. 12.6	Y Y Y	Important in drug monitoring interpretation. Decreased albumin concentration in pregnancy implicated.	Perucca <i>et al.</i> , 1981
	Chronic cardiac failure	≈15 vs. 15	N	Not significant.	Fitchl <i>et al.</i> , 1983
	Acute uraemia Chronic uraemia	10 vs. 25 10 vs. 24	Y Y	Important clinically in drug monitoring, although free conc. remains the same due to pharmacokinetic compensation.	Tiula and Neuvonen, 1986

Table 2. CONTINUED

Drug	Disease	% free or free fraction (control vs. patient)	Sig. diff.	Clinical sig./comment	References
Prednisolone	Age-related decrease in renal function	10 vs. 13.5	Y	Important in drug monitoring.	Tiula and Elfving, 1987
	Porto-systemic shunt	17.7 vs. 28.6	Y	Not significant as elimination and $V_d$ altered, therefore, normalising free conc.	Bergrem <i>et al.</i> , 1983
	Nephrotic syndr.	$2.26 \times 10^3$ vs. $4.20 \times 10^3 \text{ M}^{-1}$ $2.12 \times 10^7$ (albumin $K_a$ ) vs. $3.44 \times 10^7 \text{ M}^{-1}$ (transcortin $K_a$ )	Y N	Not known. Altered pharmacokinetic disposition, due to change in binding.	Frey and Frey, 1984
Propranolol	Chronic cardiac failure	14 vs. 14	N	AGP binding not affected.	Fitchl <i>et al.</i> , 1983
	Cancer, MI and IHD, infection, heart failure, COPD, CVA, miscell.	10.8 vs. 5.5	Y	Not clinically significant but may be important when interpreting drug levels.	Paxton and Briant, 1984
Salicylate	Acute uraemia	10 vs. 9	N	Not significant.	Tiula and Neuvonen, 1986
	Chronic uraemia	10 vs. 8.9	N	Not indicated.	
Sulphadiazine	Acl. hepatitis	27 vs. 34	N	Not known. Bilirubin and hypoalbuminaemia implicated in binding defect.	Brodie and Boobis, 1978
	Alc. cirrhosis	27 vs. 41	Y		
Sulphisoxazole	Alc. hepatitis	46 vs. 58	Y	Not known. Bilirubin and hypoalbuminaemia implicated in binding defect.	Brodie and Boobis, 1978
	Alc. cirrhosis	46 vs. 51	N		
Theophylline	Uraemia	5.2 vs. 21.8		Not indicated. Carbamylation of drug binding site I implicating in defect; site II not affected.	Calvo <i>et al.</i> , 1982
Tolfenamic acid	Acute illness in COPD	54.6 vs. 69.7 7.4 vs. 8.1 ( $\mu\text{g/ml}$ )	Y N	Not significant as free concentration is not changed significantly.	Zarowitz <i>et al.</i> , 1985
	Renal disease	0.08 vs. 0.17	Y		Laznicek and Senius, 1986
	Liver disease	0.08 vs. 0.29	Y	Not clear. High affinity for red blood cells means that these may act as reserve binding sites when free fraction increases.	

Table 2. CONTINUED

Drug	Disease	% free or free fraction (control vs. patient)	Sig. diff.	Clinical sig./comment	References
Valproic acid	Renal disease	8.4 vs. 20.3	Y	Not clear. May lead to increased incidence of toxicity. Important in drug monitoring interpretation.	Gugler and Mueller, 1978
	Early pregnancy**	9.4 vs. 11.5	Y	Important in drug monitoring. Decreased albumin serum concentration implicated in binding defect.	Perucca <i>et al.</i> , 1981
	Mid pregnancy	9.4 vs. 12.1	Y		
	Late pregnancy	9.4 vs. 14.6	Y		
	IDDM	6.2 vs. 7.6	Y	Not significant if diabetes is well controlled. If poorly controlled increased free conc. may be greater.	Gatti <i>et al.</i> , 1987
Verapamil	Arrhythmia	—	—	Not indicated. Pharmacokinetic change may be implicated.	McGowan <i>et al.</i> , 1982
	Liver disease	0.099 vs. 0.16	Y	Clinical end point effective to titrate dose so change not significant in therapy. Change may be relevant when interpreting kinetic data and total drug concentrations.	Giacomini <i>et al.</i> , 1984
Warfarin	Chronic cardiac failure	1 vs. 1	N	No change expected.	Fitch <i>et al.</i> , 1983
	NIDDM	1.1 vs. 1	N	Not indicated (but no change expected).	O'Byrne <i>et al.</i> , 1988
Zomepirac	Uraemia	1.4 vs. 4	Y	Decrease due to endogenous inhibitors. Not clinically significant.	Pritchard <i>et al.</i> , 1983

Y, yes; N, no; MI, myocardial infarction; Transpl, transplant; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; CVA, cerebro-vascular accident; AGP,  $\alpha_1$ -acid glycoprotein;  $K_a$ , drug-protein association constant; miscel, miscellaneous;  $V_d$ , apparent volume of distribution; Alc, alcoholic; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

\*Source: McElnay (1996).

\*\*Although pregnancy is not a disease, it can give rise to changed binding; therefore it has been included in this table.

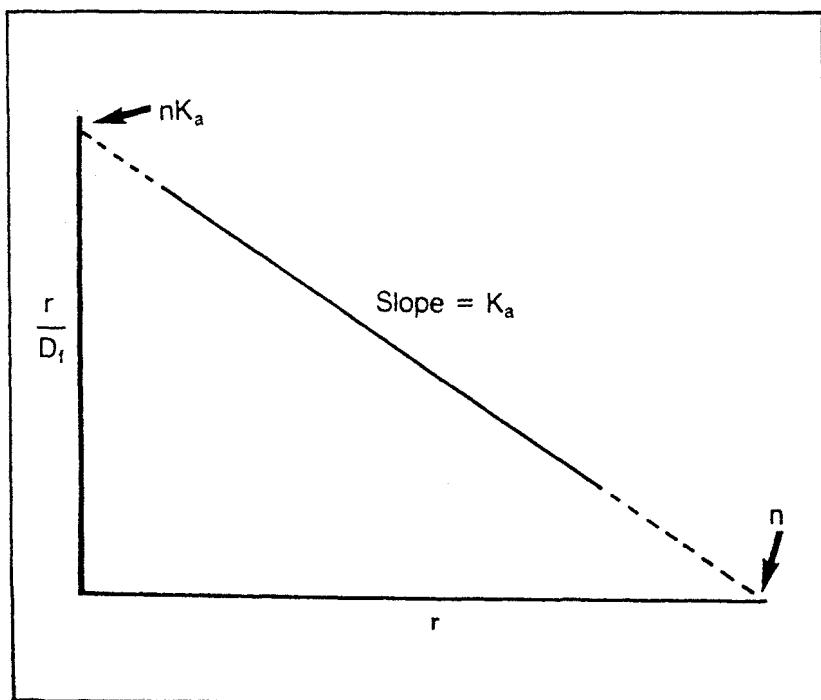


Fig. 2. Plot devised by Scatchard (1949) for drug/macro-molecule interaction for a single class of binding site ( $r$  = moles of drug bound per mole of protein;  $D_f$  = molar free drug concentration;  $n$  = number of primary binding sites). If more than a single class of binding site is involved in the binding interaction, the plot will be curved.

bind to the apozone locus (site I) and to a lesser extent to the diazepam site (site II) (Bree *et al.*, 1990). The strength of binding is measured in terms of the association constant between drug and protein, the larger the association constant the more avid the binding (D'Arcy and McElnay, 1982).

A drug may have different classes of binding sites with different affinities, e.g. tolbutamide has been estimated to have 2.27 primary binding sites (with an association constant of  $21.86 \times 10^4 \text{ M}^{-1}$ ) and 8.21 secondary binding sites (with an association constant of  $1.71 \times 10^2 \text{ M}^{-1}$ ) per molecule of albumin (Crooks and Brown, 1974). If a drug has only one class of binding site, a straight line plot is achieved in the graphical representation devised by Scatchard (Fig. 2), which having binding data over a range of protein and/or drug concentrations, can be used to determine ' $n$ ' (number of binding sites per molecule of protein) and ' $K$ ' (association constant). The graph becomes curved if more than one class of binding site is involved and the interpretation becomes difficult (McElnay, 1996). The difficulties involved in interpreting binding data have been addressed by Plumbridge *et al.* (1978).

The chirality of drugs has raised current interest in relation to interactions with receptor sites and in the difference of pharmacological actions produced by different optical isomers of the same compound. Binding of drugs to plasma proteins can

also be stereoselective. There are two illustrative examples with the isomers of propranolol and verapamil.

The difference of binding of the R- and S-isomers of propranolol in maternal, but not foetal, serum has been shown to be significant, with the R/S ratio being significantly larger in the mother than in the foetus. For verapamil, the difference in binding of the R- and S-isomers was significant in both the mother and the foetus, although the R/S ratio was similar in both (Belpaire *et al.*, 1995).

Although the protein binding of drugs primarily involves albumin, other agents are also involved; they have been summarized by McElnay (1996) as: digoxin which binds strongly to cardiac muscle; bilirubin binds with ligandin; some cytotoxics bind to the DNA; many drugs are bound by melanin; some drugs are bound to red blood cells, which recent studies have shown to have at least three binding sites (Hasegawa *et al.*, 1994).

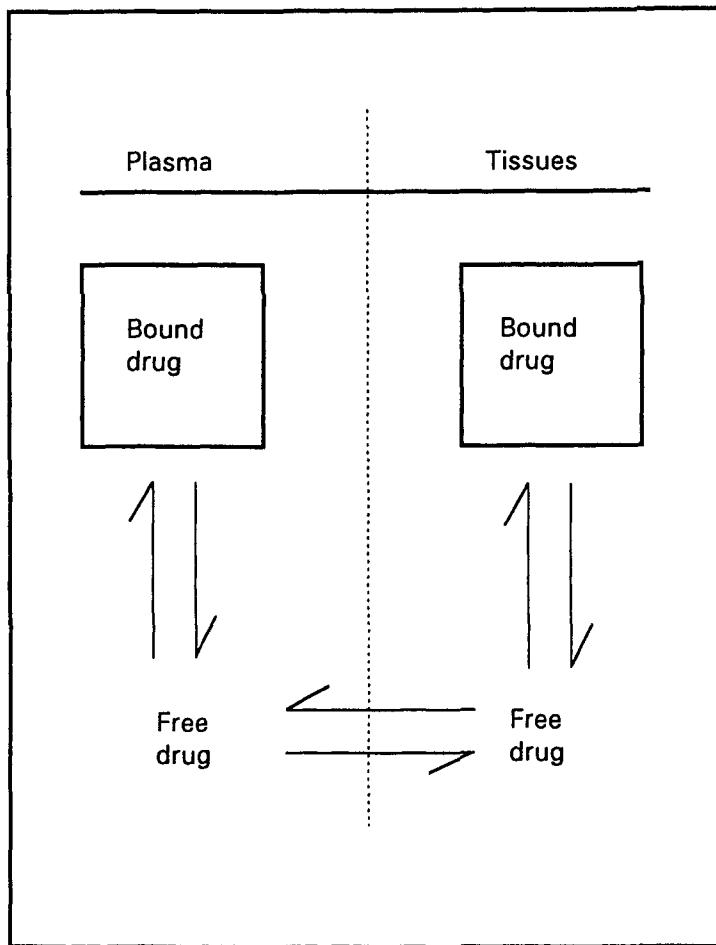
## **INFLUENCE OF PLASMA AND TISSUE BINDING ON DRUG KINETICS**

### **i. Absorption**

Both plasma and tissue binding of drugs will favour a more rapid absorption of drugs from the intestine or the injection site. These effects are, however, very marginal in comparison with the influence of protein binding on drug distribution and elimination. Plasma and tissue protein have opposing effects on drug distribution. Since plasma proteins are largely retained within the plasma compartment, drugs which are highly bound to plasma proteins tend to have low apparent volumes of distribution ( $V_d$ ). Warfarin, for example, which is highly bound to plasma albumin (>99%) has a low  $V_d$  (0.11/kg) indicating poor diffusion into the tissues (Tillement *et al.*, 1978). Drugs which are highly bound to tissues tend to have a high  $V_d$ . For drugs which are highly bound to plasma and tissues, the  $V_d$  will depend on the relative binding in both sites. For example with tricyclic antidepressants and phenothiazines almost all the drug in the plasma is bound to albumin, however, due to extensive tissue binding of these drugs, the circulating drug in plasma represents only a small fraction of the total drug in the body (Koch-Weser and Sellers, 1976). The equilibrium which exists between tissue and plasma binding is represented in Fig. 3. Only unbound drug is able to diffuse to receptor sites and exert therapeutic effects.

### **ii. Elimination**

Drug elimination involves primarily the liver and kidneys, therefore if a drug is highly bound to tissues it will be protected against elimination since much of the drug will be outside the plasma compartment and will therefore not be delivered to the liver or kidneys for elimination. In addition, the extent of plasma protein binding can have marked effects on drug clearance by these organs. Consider first drug metabolism. For most drugs, plasma protein binding is protective in that the affinity for plasma binding sites exceeds that for metabolizing activity. It is therefore



*Fig. 3.* Distribution of drug between plasma and tissue compartments. Only free (pharmacologically active) drug can diffuse out of the plasma; the equilibrium would therefore move towards the right after displacement from plasma binding and toward the left after displacement from tissue binding sites. Free drug concentrations in the plasma and tissue compartments are equal. Quantities of drug bound will depend on the amount of binding materials present in both plasma and tissues and their respective binding capacities (after Tillement *et al.*, 1980).

only free (unbound) drug that is metabolized during passage through the liver (or other metabolic site). Such drugs would be considered to have a low hepatic extraction ratio. Conversely if a drug has a high extraction ratio, the attraction to metabolic enzyme systems in the liver will overcome the binding affinity for plasma proteins and bound drug will be stripped from the binding sites to undergo metabolic change (McElnay and D'Arcy, 1983).

A similar process applies to the kidneys. Glomerular filtration is a passive process and only allows free (unbound) drug to pass through the glomerulus because protein molecules are too large to be filtered. Plasma protein binding therefore protects a

drug against elimination by glomerular filtration. Although glomerular filtration is the main mechanism of drug elimination via the kidneys, a number of drugs (e.g. penicillins) are actively secreted in the tubular urine. In summary, plasma protein binding tends to facilitate elimination by limiting drug distribution, thereby allowing more drug to be presented to the kidneys for elimination (McElnay, 1996).

### **DISPLACEMENT OF DRUGS FROM BINDING SITES**

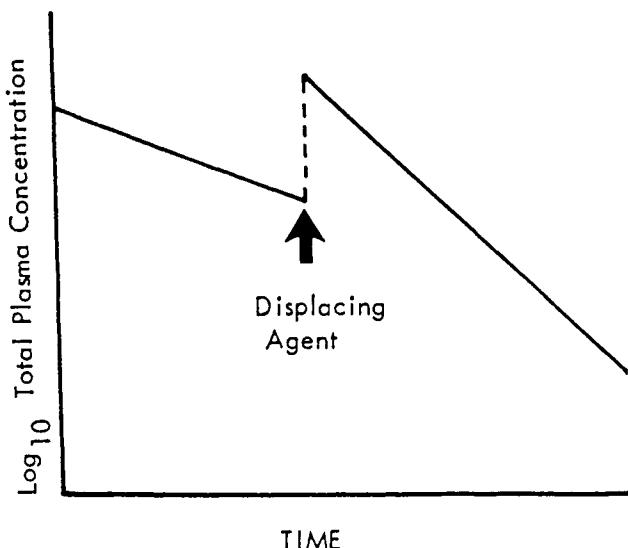
Most displacement of drugs from plasma binding sites is via a direct competition of the two drugs involved for the same binding sites. Drugs with a higher association constant will displace drugs with a lower association constant at common binding sites. The displacement of warfarin by phenylbutazone is a good example of this type of interaction. As well as the competitive displacement interactions, the binding of one drug to, for example, albumin, can give rise to changes in the conformation of the protein and so change the shape of the binding sites for a second drug.

Acetylsalicylic acid influences the binding of certain drugs, e.g. flufenamic acid and phenylbutazone by this non-competitive mechanism via permanently acetylating lysine residues of albumin (Pinkard *et al.*, 1973). Other examples of this type of displacement have been given by McElnay (1996) in his review.

### **THERAPEUTIC CONSEQUENCES OF INTERACTIONS INVOLVING DRUG DISPLACEMENT**

Two well-known interactions: (i) between tolbutamide and sulphonamides (Christensen *et al.*, 1963); and (ii) between warfarin and phenylbutazone (Agpler *et al.*, 1967) which, respectively, increased the hypoglycaemic effect of tolbutamide, and significantly increased prothrombin time, triggered off clinical interest in displacement interactions and plasma binding displacement was heralded as an important interaction mechanism. The problem with these reports is that the work was carried out *in vitro*, and whereas displaced drug cannot distribute further than the confines of the dialysis cell, in the *in vivo* situation the displaced drug can distribute out of the plasma compartment into the relatively large sink of tissues. This moves the equilibrium situation shown in *Fig. 3* in an anticlockwise direction. In addition, increased amounts of free drug will be presented to sites of elimination (liver and kidneys) immediately after displacement has occurred.

These compensatory effects of redistribution and increased elimination of free drug lead only to a transient increase in free (active) drug in the plasma, whilst at equilibrium (steady-state) the free concentration of the drug will equate to pre-interaction levels. In addition, since distribution from drug to its receptor in the plasma is often not instantaneous, but via a first-order process with comparable rate to general drug distribution, this will also reduce the extent of the transient increase in effect of the displaced drug. If the displacer drug is given orally, rapid compensatory effects may prevent even the transient increase in free drug concentration from taking place. This displacement does, however, lead to important changes



*Fig. 4.* Typical plasma concentration time profile for a drug interaction involving tissue binding displacement. An almost immediate increase in total plasma concentration (due to a decrease  $V_d$ ) is seen. Elimination half-life is shown to be increased. This is because of increased amounts of both free and bound drug being presented at sites of elimination (after D'Arcy and McElnay, 1982).

in the displaced drugs apparent volume of distribution (increased), the total concentration of drug in plasma (decreased, *Fig. 4*) and the free fraction of drug in plasma (increased). This means that the same pharmacological effect will be achieved from a reduced total (free and bound) serum concentration of the drug (McElnay, 1996).

It follows therefore that the interactions which in the past have been attributed solely to plasma binding displacement must have a different underlying mechanism. The best example of this is the warfarin–phenylbutazone interaction. As long ago as 1974, Lewis *et al.* discovered a metabolic mechanism for this interaction. Phenylbutazone was shown to stereo-selectively inhibit the metabolism of the S-isomer of warfarin which is some five to six times more potent than the R-isomer and there was a corresponding increase in the elimination of the R-warfarin. The increased proportion of the more potent S-warfarin gave rise to increased anticoagulation.

Azapropazone gives rise to markedly increased prothrombin times when administered together with warfarin (Powerl-Jackson, 1977). Although azapropazone is a powerful displacer of warfarin from plasma binding sites (McElnay and D'Arcy, 1980), this displacement cannot explain the increased pharmacological effect seen and, although it has never been investigated, it would appear that a metabolic

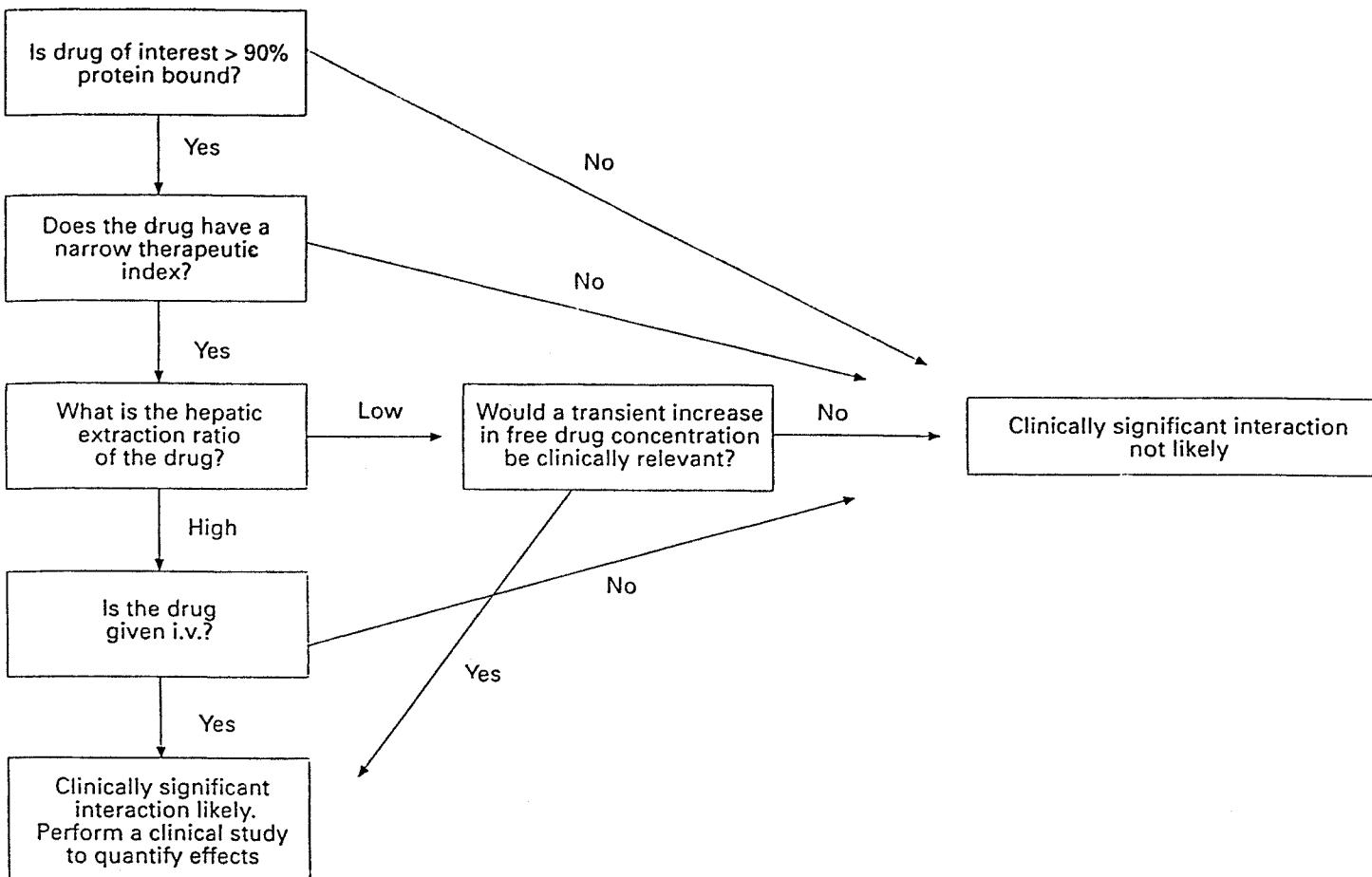


Fig. 5. Algorithm for determining clinical significance of potential plasma protein binding displacement interactions (after Rolan, 1982).

effect similar to that with phenylbutazone takes place (azapropazone has structural similarities to phenylbutazone).

In his review on drug interactions in plasma and tissue binding sites, McElnay (1996) has described other interactions which were initially described as being due to plasma-binding displacement and which now have been demonstrated to have other mechanisms responsible for the interaction. These include: warfarin/sulphamethoxazole and sulphapyrazone; methotrexate/salicylate; phenytoin/valproate, and tolbutamide/sulphonamide interactions.

Although in most cases plasma-binding displacement interactions *per se* do not give rise to clinically significant interactions, McElnay (1996) has described three main exemptions to this general rule, namely when there is a rapid infusion of a displacing drug; when there is parenteral administration of a displaced drug having a high extraction rate, and in therapeutic drug monitoring.

### COMMENT

Generally, therefore, although current opinion accepts that the binding of drugs to protein is an important pharmacokinetic parameter, it is of the view that its importance as a mechanism of drug-drug interaction has been overestimated and overstated since the effects are of a transient nature. It is only considered to be problematic with regard to adverse clinical outcomes under specific conditions. Drug interactions which in the past have been attributed to plasma binding displacement have another underlying mechanism usually involving decreased elimination of the drug in the liver or kidney. Rolan (1994) has drawn up an algorithm to help assist in determining whether displacement interactions are likely to be clinically significant. A copy of this algorithm is shown in *Fig. 5*.

### **3. DRUG INTERACTIONS AND DRUG-METABOLIZING ENZYMES**

Induction or inhibition of the collection of isoenzymes, collectively known as cytochrome P450 enzymes, are mechanisms that have been shown to underlie some of the more serious drug-drug interactions (*Tables 3 and 4*). Many such interactions can be explained by alterations in the metabolic enzymes that are present in the liver and other extra-hepatic tissues. Cytochrome P450 is not a single species of protein, the system is actually a collection of isoenzymes, all of which possess an iron atom in a prophyrin complex. At current time some 154 cytochrome P450 genes have been characterized from humans, animals, insect and plant species. They catalyse different types of oxidation reactions and under certain circumstances may catalyse other types of reaction such as reduction (Timbrell, 1993).

Since the early experiments of Conney and co-workers (Conney *et al.*, 1956, 1957; Conney, 1967) it has often been observed that the rate of oxidative metabolism of various substances can differ markedly depending on the age, sex, species or the extent of exposure of the animal to different inducing agents. A number of investigators have directed studies to evaluate the number and types of cytochrome P450s that exist in a single organ. In particular they questioned whether specific types of reactions catalyzed by the microsomal electron transport system required specific cytochrome P450, or whether many cytochrome P450s have a broad substrate specifically differing only in the rate of catalysis of each reaction.

Since the early studies of the 1950s more than 800 different xenobiotics, many of which are therapeutic drugs, have been shown to be substrates for liver microsomal oxidative enzymes. The major types of oxidation reaction catalyzed by the cytochrome P450 system can be subdivided into oxidation or hydroxylation (e.g. many drugs including paroxetine), deamination (e.g. amphetamine), dealkylation (e.g. morphine), sulphoxidation (e.g. chlorpromazine, paroxetine), desulphuration (e.g. thiopentone), dehalogenation (e.g. halogenated anaesthetics) and glucuronidation (e.g. paroxetine).

Certain oxidative reactions of xenobiotics are also catalyzed by enzymes other than the cytochrome P450 monooxygenase system. For example alcohols may be oxidized by alcohol dehydrogenase; xanthine oxidase catalyzes the oxidation of nitrogen heterocyclics such as the purine hypoxanthine. Some amines such as tyramine are substrates for monoamine oxidases; diamines such as putrescine are metabolized by the soluble enzyme diamine oxidase. The peroxidases are also involved in the oxidation of xenobiotics, the most important being prostaglandin synthase, which is known to catalyze the oxidation of *p*-phenetidine, a metabolite of phen-

## 26 A MANUAL OF ADVERSE DRUG INTERACTIONS

*Table 3. SOME EXAMPLES OF COMPOUNDS AND DRUGS ACTING AS ENZYME INDUCERS*

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### Alcohol

Chlorinated hydrocarbon pesticides

Polycyclic hydrocarbons (e.g. dioxin) and other environmental pollutants

### Tobacco smoking

Many therapeutic drugs, including:

- barbiturates
  - carbamazepine
  - carbenoxolene
  - ciprofloxacin
  - clofibrate
  - glucagon
  - glucocorticoids (e.g. dexamethasone)
  - isoniazid
  - phenylbutazone
  - phenytoin
  - primidone
  - rifampicin
  - theophylline
- 

*Table 4. SOME EXAMPLES OF COMPOUNDS AND DRUGS ACTING AS ENZYME INHIBITORS*

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### Cobalt chloride

Industrial solvents (e.g. carbon tetrachloride, dimethylformamide, etc.)

### Organophosphorus compounds

Many therapeutic drugs including:

- allopurinol
  - amiodarone
  - chloramphenicol
  - cimetidine
  - corticosteroids
  - cyclophosphamide
  - danazol
  - dextropropoxyphene
  - dicoumarol
  - erythromycin
  - felbamate
  - fluconazole
  - glibenclamide
  - influenza vaccine
  - iproniazid
  - itraconazole
  - ketoconazole
  - MAOI-antidepressants
  - moricizine
  - nicoumalone
  - 4-quinolones and fluoroquinolone antibiotics (e.g. ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, ofloxacin, perflloxacin)
  - selegiline
  - serotonin re-uptake inhibitor antidepressants (SRIs)
  - tamoxifen
  - triacetyloleandomycin
-

Table 5. CYTOCHROMES P450 IN HUMANS (BASED ON GONZALEZ, 1993)\*

Subfamily	Members	Chromosome (locus)	Established Functions/activities	Induced by
			Metabolizes	
CYP1A1	CYP1A1 CYP1A2	15q22-qter	aflatoxin B1 arylamine and its promutagens acetaminophen benzo[ $\alpha$ ]pyrene caffeine food mutagens phenacetin warfarin	Ketoconazole Omeprazole Polycyclic aromatic hydrocarbons Tobacco smoke
CYP2A	CYP2A6 CYP2A7	19q12- 13.2	aflatoxin B <sub>1</sub> <i>N</i> -nitrosodiethylamine warfarin	
CYP2B	CYP2B6 CYP2B7	19	warfarin	Phenobarbitone
CYP2C	CYP2C9 CYP2C10 CYP2C17  CYP2C18 CYP2C19	10q24.1- 24.3	mephentoin tolbutamide  warfarin	
CYP2D	CYP2D6 CYP2D7P CYP2D8P	22q11-2qter	debrisoquine sparteine nitrosamine carcinogen (NNK)	Tobacco smoke
CYP2E	CYP2E1	10	acetone caffeine chlorzoxazone paracetamol solvents <i>N</i> -nitrosodimethylamine	Ethanol
CYP2F	CYP2F1	19	naphthylamine	
CYP3A	CYP3A3 CYP3A4 CYP3A5 CYP3A7	7q21-22.1	aflatoxins benzo[ $\alpha$ ]pyrene cyclosporin erythromycin 17-ethinyloestradiol lidocaine midazolam nifedipine quinidine warfarin	Dexamethasone Steroids

\*Other cytochrome P450s have been detected in animals; multiple gene conversions have occurred among some animal CYP genes rendering them quite dissimilar to their counterparts in humans.

acetin, a process that may be involved in the nephrotoxicity of the drug (Timbrell, 1993).

During the last 10 years or so, a vast amount of work has been done on the identification and characterization of human xenobiotic-metabolizing cytochrome P450s. Black (1993) has reviewed the cytochrome P450 structure and function and Gonzalez (1993) cytochrome P450 in humans. Mammalian P450 enzymes are tightly bound in both microsomes (endoplasmic reticulum) and mitochondria. Purified preparations exhibit a high amphiphilic character and exist as micellar aggregates of approximately six protomers (Dean and Gray, 1982). The enzymes are discrete gene products of about 57 000 molecular weight and contain one equivalent of b-type heme per polypeptide.

The most abundantly expressed cytochrome P450s in human liver are the CYP3A family; other subfamilies in human tissues are CYP1A, CYP2B, CYP2C, CYP2E, and CYP2F. The locus, function and activities of these are shown in *Table 5*. Cytochrome P450 is the subject of an excellent and comprehensive book by Schenckman and Greim (1993) and an article specifically dealing with drug interactions and drug-metabolizing enzymes has been prepared by D'Arcy (1996).

## **4. INTERACTIONS INVOLVING RENAL EXCRETORY MECHANISMS**

Interactions involving renal excretory mechanisms can have important clinical implications in terms of patient mortality and morbidity. It is fortunate that an understanding of the molecular mechanisms of renal drug transport has allowed predictions to be made of potential drug interactions in early phase drug development. This understanding together with the availability of *in vitro* models of renal drug transport has also been used as an early guide to potential *in vivo* drug interactions.

The kidney represents the final elimination organ for virtually all foreign substances irrespective of whether they are cleared unchanged or as metabolites formed in the body predominantly by the liver. Somogyi (1996) has reviewed drug interactions involving renal excretory mechanisms and much of the following text is summarized from his comprehensive account.

The functional unit of the kidney is the nephron (*Fig. 6*), which filters, secretes and resorbs molecules. Glomerular filtration (ca. 120 ml/min) involves the forcing of fluids containing dissolved substances through the endothelial-capsular membrane. This membrane, which acts as a filter, allows some materials to pass through whilst restricting the passage of others. The resulting filtrate is free of protein and substances with a molecular weight of greater than 40 000 and about 20 Å in diameter. The mechanism by which drugs can interact at the glomerulus are:

(i) Displacement from protein-binding sites. The pharmacokinetic consequence of this will be that unbound fraction of drug in the plasma will increase and clearance of the drug by the glomerulus will also increase in direct proportion to the increase in the unbound fraction. There are very few examples in the literature of drug-drug interactions occurring exclusively at the glomerulus (Somogyi, 1996).

(ii) Where the glomerulus is physically damaged through, for example, the nephrotoxic action of a xenobiotic. In such a case, the maximum clearance of a drug will be equal to the glomerular filtration rate, irrespective of the value of the drug's unbound fraction. This type of interaction is poorly documented and would rarely occur on its own (Somogyi, 1996).

The blood flow to the kidney then passes to the tubular network where active transport systems are capable of removing drugs and endogenous substances from blood and secreting them into the lumen of the kidney. This occurs at the site of the proximal tubule, where there are a number of transporters for organic anions and cations. Specific transporters for these anions and cations occur at both the

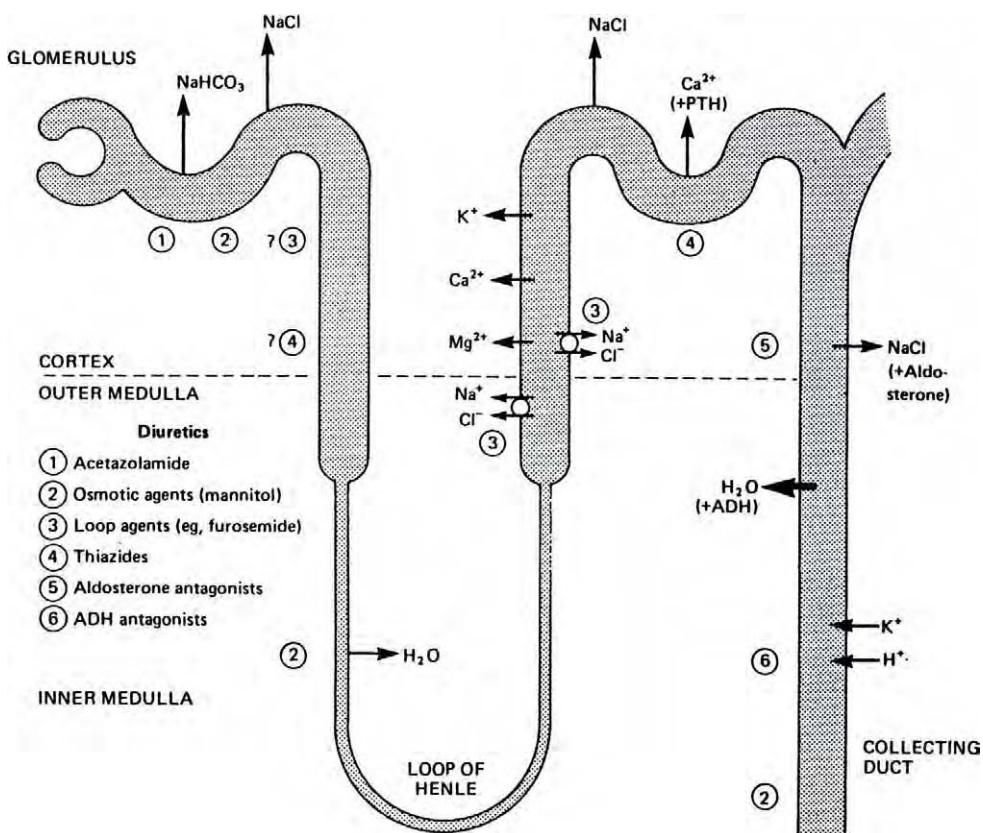


Fig. 6. Tubule transport systems and sites of action of diuretics. (Source: Warnock, 1982)

luminal (brush border) and contraluminal membranes of the epithelial cells lining the proximal tubule (Somogyi, 1996).

The transport process for organic anions has been reviewed by several groups (Møller and Sheikh, 1983; Ullrich, 1994; Somogyi, 1996); although not fully evaluated in humans, the renal transporter of organic anions (*p*-aminohippuric acid being the most commonly used probe substrate) is located at the contraluminal membrane. The cellular uptake of organic ions has been termed a tertiary active transport process since the primary transporter is the ATP-dependent sodium/potassium transport step, which activates a sodium-dicarboxylate transporter, creating an *ketoglutarate* gradient which is exchanged for the organic ion (Somogyi, 1996).

The transport process for organic cations has been reviewed by Peters (1960); Rennick (1981) and Somogyi (1996). Secretion of organic cations across the mammalian kidney occurs along the entire length of the proximal tubule. At the contraluminal membrane there is evidence for one common transport system. At the luminal membrane, the transport of organic cations occurs by an electroneutral  $\text{H}^+$ /organic cation system. The driving force at this luminal interface is the sodium/hydrogen

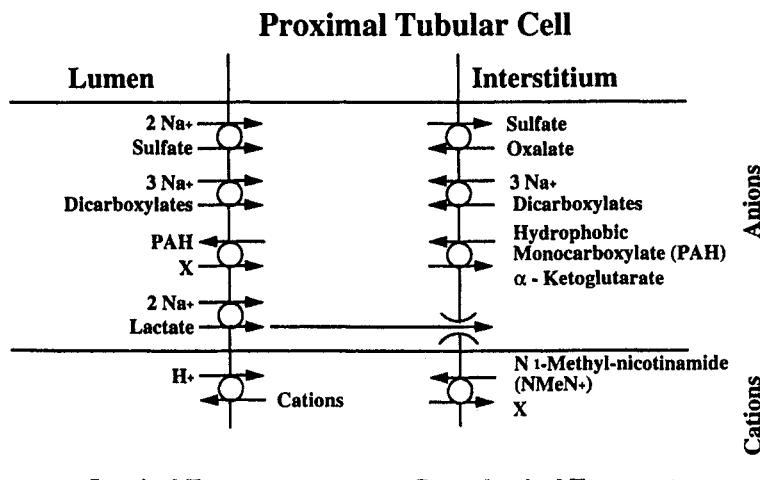


Fig. 7. Location of transporters for organic anions and cations in the renal proximal tubule (from Ullrich (1994)). Note: PAH is the organic anion *p*-aminohippuric acid.

transporter, which transports sodium ions into the cell and hydrogen ions out (Fig. 7) (Somogyi, 1996).

A key feature of a drug undergoing tubular secretion is that it will compete with another drug for secretion, thus competition for transport is competitive. The drug with the higher affinity for the transporter will be a more potent inhibitor of the transport of a similar chemical substance for the same transporter. Hence organic anions will compete with one another for transport (e.g. probenecid and penicillin) and organic cations will compete with one another (e.g. cimetidine and procainamide). This is the most common type of drug-drug interaction involving renal excretory mechanisms (Somogyi, 1996).

As the drug passes down the tubular lumen into the distal tubule and collecting duct, passive diffusion of drug takes place driven by the concentration gradient of drug across the cellular membrane back into the blood. The process of passive reabsorption is applicable to the unionized lipid-soluble form of the drug. Thus the  $pK_a$  of the drug and the pH of the tubular fluid become important, as only the unionized form is sufficiently lipid soluble to diffuse through the epithelial membranes of the tubule cells. Hence any drug which alters urine pH or urine flow rate (which alters the concentration gradient) has the potential for altering the tubular resorption of other drugs. The significance of any interaction at this site is often of minor importance since the basic requirement is the degree of lipid solubility of the drug and, in general, lipid-soluble drugs are extensively metabolized by the liver rather than being extensively cleared by the kidney. Exceptions to this include the ephedrine series, salicylates and chlorpromazine (Somogyi, 1996).

## TUBULAR SECRETION

Of the mechanisms for renal drug excretion, drug interactions predominantly involve tubular secretion. The most commonly investigated interacting drug has been

## 32 A MANUAL OF ADVERSE DRUG INTERACTIONS

Table 6. SOME INTERACTIONS INVOLVING RENAL CLEARANCE\*

### **Amiodarone–procainamide**

Amiodarone reduced the total body clearance of procainamide by 23%. This appears to be predominantly due to renal clearance, most likely as a consequence of competition for active tubular secretion.

### **Cimetidine–amiloride**

Cimetidine reduced the renal clearance of amiloride by 17% but did not affect the area under the plasma amiloride concentration-time curve.

### **Cimetidine–cephalothin/cephalexin**

Cimetidine had no effect on the renal clearance of the organic anion cephalothin, however, it reduced the renal clearance of the zwitterion cephalexin by 20%. It was concluded that cimetidine's effect was specific for organic cations and that both anion and cation transport systems might be involved for those zwitterions that undergo tubular secretion.

### **Cimetidine–metformin**

Cimetidine increased the area under the plasma metformin concentration-time curve by an average of 50%, this was associated with a 27% reduction in the renal clearance of metformin.

### **Cimetidine–nicotine**

Cimetidine reduced the renal clearance of nicotine by approximately 50% but did not affect the renal clearance of the metabolite cotinine.

### **Cimetidine–pindolol**

Cimetidine increased the area under the plasma pindolol concentration-time curve ( $R(+)$  10%;  $S(-)$  26%) and reduced its renal clearance. The enantiomer with the higher renal clearance  $S(-)$  pindolol had a smaller (mean 26%) cimetidine-induced reduction in renal clearance compared with the  $R(+)$  pindolol (34%). Cimetidine had a stereoselective inhibitory effect on the active transport of organic cations in the proximal tubule.

### **Cimetidine–procainamide–acetylprocainamide**

Cimetidine increased the area under the plasma concentration-time curve of procainamide by 44% and prolonged the half-life by 26% due to a marked reduction in the renal clearance of procainamide (44%). The AUC for acetylprocainamide was increased by 25% with a commensurate reduction in renal clearance of 24%. These data reinforced the mechanism of competitive inhibition of tubular secretion of procainamide by cimetidine.

### **Cimetidine–quinidine**

Cimetidine reduced the renal clearance of quinidine by 36%.

### **Cimetidine–ranitidine**

Cimetidine increased the area under the plasma ranitidine concentration-time curve, this was associated with a 25% reduction in the renal clearance of ranitidine.

### **Cimetidine–triamterene**

Cimetidine increased the area under the plasma triamterene concentration-time curve, this was associated with a 70% reduction in the renal clearance of triamterene.

### **Digoxin–amiodarone**

Amiodarone reduced the renal clearance of digoxin by 2%; it also reduced its non-renal clearance. The reduction in renal clearance of digoxin was interpreted as a reduction in its tubular secretion.

### **Digoxin–spironolactone**

Initial studies showed that spironolactone decreased the renal clearance of digoxin by 30%, as there was no effect on the glomerular filtration rate the mechanism remained unexplained. Later studies confirmed these results but the mechanism still remains unclear although it has been suggested to be due to increased potassium in distal tubular cells increasing digoxin secretion.

*Table 6. CONTINUED***Digoxin-quinidine**

Several mechanisms, including a reduction in digoxin renal clearance (35%), are thought to be involved in this interaction. The reduction in renal clearance is consistent with the competition for active tubular secretion. Since quinidine has no effect on glomerular filtration rate, the results of these studies have been interpreted as a reduction in the tubular secretion of digoxin by quinidine. It is possible that both digoxin and quinidine compete for the same carrier-mediated transport system in the kidney.

**Digoxin-verapamil/other calcium antagonists**

Verapamil increases plasma digoxin concentrations and evokes toxicity, in some cases fatal. The mechanism is thought to be due to a reduction in the renal clearance of digoxin, although this has been disputed. Recent studies suggest that the effects of verapamil on digoxin renal clearance may be transient and may be confounded by alterations in urine flow rate. Most studies with diltiazem or nifedipine have resulted in contradictory findings and the magnitude of any changes in the disposition of digoxin have been small.

**Famotidine-procainamide-acetylprocainamide**

Famotidine had no effect on the total body or renal clearance of procainamide or its metabolite.

**Quinine/quinidine-amantadine**

Quinine and quinidine had no significant effect on amantadine renal clearance in either young or old subjects. However, when the data were separated according to gender both agents significantly reduced the renal clearance of amantadine in males but not in females. It was suggested that testosterone might enhance the renal organic anion and cation transport system of xenobiotics.

**Ranitidine-nicotine**

Ranitidine had no effect on the renal clearance of nicotine or cotinine.

**Ranitidine-procainamide-acetylprocainamide**

High dosage of ranitidine increased the area under the plasma procainamide concentration-time curve by 20% with a 35% reduction in its renal clearance. The renal clearance for acetylprocainamide was reduced by 38%. Clinical dosage of ranitidine had little effect on these indices. It was concluded that any possible effect of ranitidine on the tubular secretion of procainamide or its metabolite only occurred at plasma concentrations in excess of those produced by normal therapeutic dosage.

**Ranitidine-triamterene**

Ranitidine reduced the renal clearance of triamterene by 51%. This was interpreted as competition between ranitidine and triamterene for the renal organic cation transport system. The renal clearance of its metabolite, the sulphate conjugate or *p*-hydroxytriamterene, was reduced by 47% which raised the possibility of multitransport systems.

**Trimethoprim-procainamide-acetylprocainamide**

Trimethoprim increased steady-state plasma concentrations of procainamide by 62% and acetylprocainamide by 52%, due to their reductions in renal clearance by 47 and 13%, respectively. This interaction is consistent with trimethoprim having a higher affinity than procainamide and acetylprocainamide for the organic cation transporter and hence inhibiting their tubular secretion.

**Trimethoprim-zidovudine**

Trimethoprim reduced the renal clearance of zidovudine by 58% and in addition reduced the renal clearance of the glucuronide conjugate of zidovudine by 20%. The renal tubular secretion of zidovudine is via the organic cation transport system whilst that of its glucuronide conjugate is via both organic anion and cation systems.

\*Source: references cited by Somogyi (1996).

probencid and there are numerous published studies showing that it reduces the renal clearance of drugs that are organic anions, for example penicillins, allopurinol, enprofylline and dyphylline, frusemide, indomethacin, clofibrate, sulphapyrazone, zidovudine, acyclovir, quinolones, cephalosporins, and famotidine.

Several drug interactions have been reported involving the renal clearance of the antineoplastic methotrexate. Since the drug has a narrow therapeutic index, these interactions have on occasion been manifested by overt methotrexate toxicity. Somogyi (1996) has reviewed those drugs which interact with methotrexate, they include: probenecid, penicillins, urinary alkalinizers, NSAIDs, including aspirin, indomethacin, ketoprofen, naproxen, and ibuprofen.

With regard to organic cations, the most commonly investigated interacting drugs have been cimetidine, other H<sub>2</sub>-receptor antagonists and trimethoprim. Somogyi (1996) has reviewed the interactions by which cimetidine reduces the renal clearance of some organic cations including: procainamide, triamterene, ranitidine, amiloride, metformin, pindolol, nicotine and quinidine. Studies have also investigated whether other H<sub>2</sub> antagonists (which are organic cations) behave in a similar manner to cimetidine. Somogyi (1996) has also reviewed those interactions which occur between ranitidine and *n*-acetylprocainamide (the active metabolite of procainamide), ranitidine and triamterene, famotidine and *n*-acetylprocainamide.

Miscellaneous interaction involving renal clearance have also been reviewed by Somogyi (1996), these include trimethoprim–procainamide, *n*-acetylprocainamide, trimethoprim–zidovudine, amiodarone–procainamide, *n*-acetylprocainamide, quinine/quinidine–amantadine, and some interactions involving organic neutral drugs including digoxin–amiodarone, digoxin–spironolactone and potassium–sparing diuretics, digoxin–quinidine, digoxin–verapamil, and digoxin–other calcium antagonists. *Table 6* summarizes the nature and sequelae of all these interactions.

## TUBULAR REABSORPTION

### Proximal tubule site

#### *Lithium Salts*

The kidney is the major clearance organ for the elimination of lithium. After filtration of lithium and sodium at the glomerulus, approximately 70% of the filtered load of sodium and lithium is reabsorbed at the proximal tubule, which does not distinguish between these two inorganic ions. A number of drugs alter the elimination of lithium by altering its renal clearance. These include NSAIDs and thiazide and possible loop diuretics, which reduce the renal clearance of lithium and sodium salts (e.g. sodium bicarbonate) and theophylline which increases the renal clearance of lithium. These interactions have been categorized by Somogyi (1996); *Table 7* summarizes their nature and sequelae.

**Table 7.** DRUGS WHICH ALTER TUBULAR REABSORPTION OF LITHIUM BY ALTERING ITS RENAL CLEARANCE\*

Loop diuretics	Increased serum lithium concentrations (61%) in 1/6 normal subjects; danger of toxicity.
Sodium salts	Failure to achieve and maintain therapeutic serum lithium concentrations.
Theophylline	Renal clearance of lithium increased (42%); decreased half-life; decrease in serum lithium concentrations (30%).
Thiazide diuretics	Renal clearance of lithium reduced (40–68%); increased serum lithium concentrations (100%); danger of toxicity.
<b>NSAIDs</b>	
Aspirin and salicylates	No significant effect on serum lithium concentrations.
Diclofenac	Decreased renal clearance (23%); increased serum lithium concentrations (26%).
Ibuprofen	Reduced renal clearance (24%); increased serum lithium concentrations (15%); reports of lithium toxicity.
Indomethacin	Reduced renal clearance (31%); increased serum lithium concentrations (43%).
Naproxen	Reduced renal clearance (20%); increased serum lithium concentrations (16%); a report of lithium toxicity in one patient.
Phenylbutazone	Small increase in serum lithium concentrations (0–15%); side-effects reported.
Piroxicam	Increased serum lithium concentrations in one patient; adverse effects reported.
Sulindac	No significant effect on serum lithium concentrations.

\*Source: references cited by Somogyi (1996).

### Distal tubule/collecting duct site

#### *Chlorpropamide, Pseudoephedrine*

Many studies have been conducted to examine the influence of urine pH or flow rate on the renal clearance of drugs via modifying passive reabsorption. Two such examples of interactions by this mechanism are quoted by Somogyi (1996): those involving the organic anion chlorpropamide and the organic cation pseudoephedrine. With chlorpropamide the area under the plasma concentration/time curve was significantly larger when the urine was made acidic by ingestion of ammonium chloride than when made alkaline by ingestion of sodium bicarbonate Neuvonen and Kärkkäinen (1983). A strong relationship was evident between the half-life of pseudoephedrine and urinary pH; at pH 5.8 the half-life was about 300 min and at pH 7.2 it increased to 600 min. There was also a significant correlation between the renal clearance and urine flow (Brater *et al.*, 1980).

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## **B. Pharmacodynamic Drug Interactions**

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## **5. DRUG-DRUG INTERACTIONS AT THE RECEPTOR AND OTHER ACTIVE SITES**

### **POTENTIALLY HAZARDOUS INTERACTIONS**

Pharmacodynamic interactions at receptor sites have been extensively reviewed by Schorderet and Ferrero (1996). Although the majority of drug-drug interactions are potentially, if not actually hazardous, some are synergistic and may be to the patients therapeutic advantage. Theoretically, at least, since such interactions are based on supposedly established mechanisms, they should be more easily prevented and should have less clinical impact than pharmacokinetic interactions. However, the relevance of such a view may be questioned in the light of recent advances in the characterization and detection of kinetic interactions.

Many of the mechanisms underlying pharmacodynamic interactions involve interference with:

- (i) Transmission systems, e.g. the noradrenergic synapse, the dopaminergic synapse, the serotonergic synapse, the cholinergic synapse and the GABAergic synapse.
- (ii) Ion channels: interactions may occur via changed affinity for or access to ion channels, e.g. calcium ion channels, potassium channels and ATP-sensitive channels.
- (iii) Hormonal systems: interactions may involve hormonal treatments (notably with corticosteroids) and glycaemic regulation.
- (iv) Homeostatic regulations: interactions in this category may involve homeostasis regulations such as renal perfusion, the production of renal prostaglandins and potassium balance.

*Table 8* summarizes drug interaction information that has been given by Schorderet and Ferrero (1996) on these mechanisms in their review.

### **SYNERGISTIC INTERACTIONS**

Not all drug-drug interactions are hazardous, and some synergistic interactions when they occur can be of clinical value in therapy. Indeed some food-drug interactions can be valuable, especially when food improves the bioavailability of the active drug substance for example taking propranolol or metoprolol with food improves their bioavailability (Melander *et al.*, 1977) and the absorption of cefuroxime axetil is improved in the presence of food (Ridgway *et al.*, 1991; Reynolds, 1993). Improvements are also seen with food in the absorption of antileprosy agent clofazimine.

Table 8. PHARMACODYNAMIC INTERACTIONS: EXAMPLES OF MECHANISMS\*

<i>Site of interaction</i>	<i>Sequelae of interaction</i>
<b>Transmitter system</b>	
Noradrenergic synapse	Amphetamine and tyramine stimulate the outward transport of noradrenaline; cocaine and imipramine block the inward transport (reuptake) of noradrenaline. $\beta$ -blockers mask the symptoms of hypoglycaemia in the medicated diabetic patient.
Dopaminergic synapse	Interaction between L-dopa and pharmacological doses of pyridoxine (vitamin B <sub>6</sub> ) is due to increased peripheral decarboxylation of L-dopa by the L-aminoacid decarboxylase cofactor which results in a decreased transfer of L-dopa to the CNS and a concomitant reduction in therapeutic efficacy.
Serotonergic synapse	Amphetamine and 3,4-methylene dioxy-methamphetamine ('ecstasy') stimulate the outward transport of serotonin, while cocaine, dextromethorphan, pethidine and the selective serotonin reuptake inhibitors (SSRIs) block the inward transport of serotonin. The combined treatment with irreversible MAOIs and SSRIs causes a serotonin syndrome.
Cholinergic synapse	Most interactions occurring at the cholinergic receptor involve additive effects between muscarinic receptor blocking drugs (e.g. atropine, carbamazepine, chlorpromazine, imipramine, ipratropium, etc.).
GABAergic synapse	Benzodiazepines, barbiturates, general anaesthetics, gabapentin, progabide, vigabatrin and probably alcohol reinforce GABAergic transmission. Potentiation of CNS depression with increased risk of respiratory depression is an example of a pharmacodynamic interaction brought about by the combination of any of these hypnotic agents. The administration of flumazenil, penicillins, quinolones, bicuculline, picrotoxin and cyclodiene insecticides inhibit GABA-mediated processes and have been reported to cause CNS stimulation or convulsions. Flumazenil is a benzodiazepine receptor antagonist and may trigger convulsions in the epileptic patient treated with benzodiazepines.
<b>ION channels</b>	
Calcium/sodium ion channels	Class I antiarrhythmic drugs have sodium channel blocking properties. The concomitant administration of anti-arrhythmic drugs with distinct properties (e.g. class Ia/Ib) may result in either adverse or beneficial interactions. As an example of the latter, mexiletine (Ib) and quinidine (Ia) in combination are more effective than each drug given alone in higher dosage. Cardiac calcium channels are concerned with the additive interaction between class II ( $\beta$ -blockers) and class IV (diltiazem, verapamil) anti-arrhythmic drugs. The resulting inhibition of atrioventricular conduction is due to the blockade of nodal calcium channels induced both directly by the calcium channel blocker and indirectly, via a reduction in sympathetic drive by the $\beta$ -blocker.
Potassium channels	<i>Torsade de pointes</i> is a potentially lethal ventricular arrhythmia which can be produced by class I and class III antiarrhythmic agents, as well as by any drug that prolongs repolarization. Synergism is likely to occur when QT-modifying drugs are given together. This is why mefloquine and halofantrine should not be used together. Electrolyte disorders caused by diuretics can precipitate <i>torsade de pointes</i> and have a synergistic effect with class Ia antiarrhythmics.

Table 8. CONTINUED

<i>Site of interaction</i>	<i>Sequelae of interaction</i>
ATP-sensitive potassium channels	ATP-sensitive K <sup>+</sup> channels of the pancreatic B-cells are the target of K-channel blocking drugs like the hypoglycaemic sulphonylureas which reduce membrane polarization. This increases the opening probability of calcium channels resulting in insulin release. On the contrary, diazoxide and somatostatin are K <sub>ATP</sub> channel openers which hyperpolarize the cell and inhibit insulin release.
<b>Hormonal system</b>	
Adrenal corticosteroids	Their metabolic effects (e.g. stimulating hepatic gluconeogenesis and decreasing peripheral utilization of glucose) which tend to produce a hyperglycaemic state will reduce the efficacy of insulin and other antidiabetic agents. Mineralocorticoids aggravate the hypokalaemia induced by thiazide or loop diuretics. They may interfere with the development of the protective immune response to vaccines.
Glycaemic regulation	Many drugs affect glycaemic regulation and can thus interfere with antidiabetic agents. For example, $\beta$ -blockers cause severe hypoglycaemia and may mask its prodromal signs. Salicylates in high dosage decrease blood glucose concentrations possibly by increasing insulin secretion.
<b>Homeostatic regulation</b>	
Renal haemodynamics and drug-induced acute renal failure	Decreased renal perfusion is a major factor that predisposes to nephrotoxicity. Besides various non-drug-related causes, renal perfusion can be decreased by drug-induced sodium and volume depletion (diuretics) or by systemic anti-hypertensive agents. With reduced renal perfusion, the glomerular hydrostatic pressure and filtration rate are maintained through a balance between angiotensin II-mediated efferent arteriole constriction and prostaglandin-effectuated afferent arteriole dilation. Thus drugs interfering with either prostaglandin synthesis (e.g. NSAIDs), or the renin-angiotensin system (e.g. ACE inhibitors) will precipitate acute renal failure.
Prostaglandins, natriuresis, and anti-hypertensive drugs	NSAIDs interfere with the production of renal prostaglandins and may reduce the natriuretic effect of concomitant diuretics, especially frusemide. NSAIDs can decrease the efficacy of most antihypertensives; piroxicam had the greatest effect whilst sulindac and aspirin were the least effective. Caution recommended with OTC NSAIDs in treated and controlled hypertensive patients.
Potassium homeostasis	All thiazides and loop diuretics increase the renal excretion of potassium. Hypokalaemia augments the risk of arrhythmias, particularly during treatment with anti-arrhythmic drugs. It also increases the toxicity of cardiac glycosides. Patients taking potassium supplements or potassium sparing diuretics who take ACE inhibitor antihypertensives have a serious risk of hyperkalaemia. NSAIDs tend to produce hyperkalaemia by interfering with renin release; this may be aggravated by taking potassium supplements or potassium-sparing diuretics.

\*Source: references cited by Schorderet and Ferrero (1996).

ine (Holdiness, 1989; Reynolds, 1993), the urinary antiseptic nitrofurantoin (Rosenberg and Bates, 1976), and the antifungal itraconazole (Van Peer *et al.*, 1989). The antifungal antibiotic griseofulvin is better absorbed in the presence of fatty foods (Crounse, 1961) or milk (Ginsburg *et al.*, 1983).

There are other examples where drug-drug interactions can improve the efficacy of therapy, for example the treatment of erythropoietin resistance with cyclosporin (Almond *et al.*, 1994). The H<sub>2</sub>-receptor blocker cimetidine binds to microsomal

P450 enzymes and inhibits the oxidative phase of hepatic drug metabolism, thus potentiating the effect and/or duration of action of a variety of drugs. These drugs include anticoagulants (e.g. warfarin), theophylline and aminophylline, some benzodiazepines, anti-arrhythmic agents (e.g. lignocaine and quinidine), anticonvulsants (e.g. carbamazepine and phenytoin), some  $\beta$ -blockers, narcotic analgesics, and tricyclic antidepressants (e.g. nortriptyline). Cimetidine also increases the bioavailability of fluorouracil by over 70% without evidence of increased toxicity (see Griffin *et al.*, 1988).

It is understandable to think that increasing the plasma concentrations of a primary drug, for example by cimetidine, will automatically and consequently increase the probability of increased toxicity of that drug. However, this may not always occur and if it does not then the dose-sparing effect on the primary drug would have both a clinical and cost advantage. There could therefore be much advantage in searching for a chemical substance which would reversibly inhibit the P450 oxidase systems without itself having a distinct pharmacological or toxicological action.

A comprehensive account of the more important treatments with believed synergistic drug combinations has been give by Griffin and D'Arcy (1996).

## **6. DRUG INTERACTIONS *IN VITRO***

Currently much information is appearing in the literature usually from pharmaceutical research sources on drug interactions *in vitro*. Much of this information in the past has been interactions between drug and drug, and drug and fluid in intravenous infusions. More recent work has concentrated on interactions between specific drugs, notably chloroquine, cyclosporin, insulin and vasodilator nitrates, and pharmaceutical packaging materials (glass and plastics), and the mechanisms by which these *in vitro* interactions occur.

Within this category are drug interactions with contact lens materials and importantly drug-excipient interactions. In the past, it has not always been appreciated that the so-called 'inactive' excipients used in product formulations are physico-chemically active substances which are often quite capable of interacting or producing complexes with drug substances in the formulation. They can cause changed absorption and altered bioavailability. The often quoted outbreak of phenytoin intoxication in Australia during 1968–9 was caused by increased bioavailability due to a simple change in capsule filler from calcium sulphate to lactose (Tyrer *et al.*, 1970).

For some time now, a great deal of effort has been given to the complexing of drug substances to a variety of polymers with the object of producing sustained-release products. Some of this research has been done with proteins, the ultimate goal being the production of an orally effective insulin.

*In vitro* interactions may be defined as those interactions which occur outside the body. Therefore this category includes interactions between drugs due to incompatibility (e.g. drug-drug interactions in an intravenous infusion), due to interaction of a drug with its container or packaging (e.g. drug binding to an infusion bag), due to loss of drugs during laboratory analyses (e.g. drug binding to laboratory equipment) or due to changes in the bioavailability of drugs when the formulation is altered (McElnay and D'Arcy, 1980). This topic has been recently reviewed by McElnay and Hughes (1996).

The sequelae of these types of interaction differ from that of the *in vivo* interactions; the *in vivo* interaction usually results in enhancement or reduction of drug efficacy or increase in drug toxicity, whereas *in vitro* interactions invariably result in reduced bioavailability (drug efficacy) during dosage. The present chapter is intended to give a general overview of these types of drug interactions which may be associated with:

- (i) additives to intravenous fluids;
- (ii) drug-container/packaging interactions;
- (iii) excipients in drug formulations; and
- (iv) a special and limited category of drug-contact lens interactions.

## INCOMPATIBILITY INTERACTIONS.

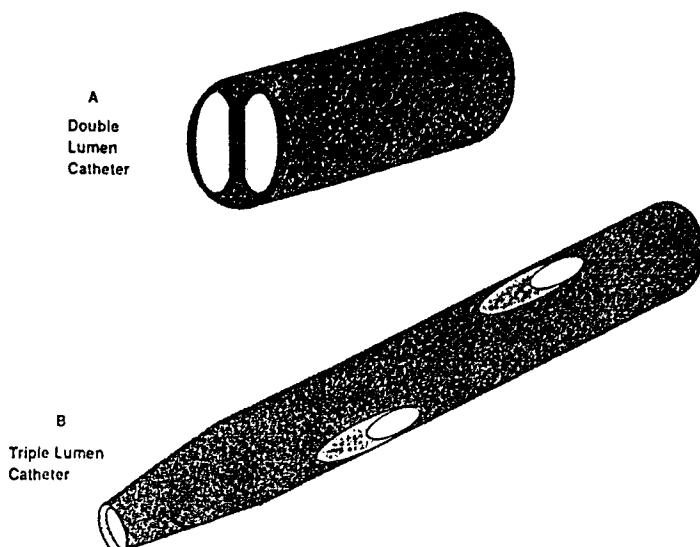
### i. ADDITIVES TO I.V. FLUIDS, MIXING DRUGS IN SYRINGES, IN LIQUID PREPARATIONS

This form of interaction is often described as an incompatibility between two agents and may be physical or chemical in nature. The interaction often occurs in solution, e.g. following addition of drugs to intravenous fluid containers, after mixing drugs in syringes or in liquid preparations for oral or topical administration.

Physical incompatibility may be due to immiscibility or insolubility, whereas chemical incompatibility may be caused by pH change, decomposition or complex formation. Many such incompatibilities are no longer viewed as being particularly problematic so far as oral formulations are concerned since easy solutions to the problems can usually be found. There are often, however, many contemporary reports in the pharmaceutical literature on drug interactions due to incompatibility in intravenous fluids. These can either be due to an interaction between two or more drugs added to intravenous fluids prior to administration or due to a single added drug being incompatible with the intravenous vehicle. We prepared a list of such incompatibilities in the previous edition of this book, it has not been updated here since the number of reports have become far too voluminous. One of the areas of medicine where simultaneous co-administration of a number of intravenous medicines is a clinical necessity is cancer chemotherapy.

Fournier *et al.* (1992) studied the effect of a commercial formulation of 5-fluorouracil on the stability of cisplatin and carboplatin to determine whether the drugs could be mixed in containers or intravenous lines. When cisplatin was incubated with 5-fluorouracil HPLC studies demonstrated a rapid disappearance of the parent platinum compound, the extent of degradation being 75% after 3.5 hr. Degradation was caused by an interaction between cisplatin and trometamol, an organic amine proton acceptor which is used as an alkalinizing agent to buffer the 5-fluorouracil solution at pH 8.2. This interaction was shown to completely inhibit the antitumour activity of cisplatin in mice. When cisplatin was incubated at the same pH in trometamol-free sodium hydroxide solutions the parent compound was transformed into an active compound that was toxic to mice. Degradation of carboplatin-trometamol admixtures was similar to that found for cisplatin, but occurred at a slower rate. It was concluded that both carboplatin and cisplatin were incompatible with 5-fluorouracil formulations containing trometamol.

Due to the possibility of incompatibility with constituents, as a general rule no drugs should be added to TPN fluids. To avoid direct contact between TPN fluids and drugs administered intravenously, Collins and Lutz (1991) have examined the



*Fig. 8. Drawings of tips of two types of catheter used in the study of concomitant administration of phenytoin and TPN fluid (after Collins and Lutz, 1991).*

co-administration of phenytoin in multilumen catheters. These devices can be used to reduce the need for frequent venipuncture and they provide a means of administering incompatible drugs. The study utilized an *in vitro* model flow system to examine the physico-chemical phenomena that occurred when these two incompatible entities (phenytoin and TPN fluid) were simultaneously administered through multicatheter systems into a circulating fluid (sodium chloride, sodium bicarbonate and albumin in solution). Double- and triple-lumen catheters were used as shown in *Fig. 8*. Video recordings were made of the drug flow and assays of phenytoin concentration were performed on samples of the circulating fluid. White clouds of phenytoin precipitation were seen near the tip of the double-lumen catheter, but not in the triple-lumen device. Infusion through the former resulted in an average of 65% loss of phenytoin which, on microscopic examination, appeared as spindle-shaped crystals. In some cases, millimetre-size fragments were seen to dislodge from the tip of the double-lumen catheter.

It was suggested that the interaction was due to the close proximity of the two orifices at the end hole of the double-lumen catheter, which permitted mixing of the two effusing streams of the incompatible agents. The staggered orifices of the triple-lumen catheter reduced this interaction greatly, no crystals were observed, although a thin coating of white film did form near the opening of the proximal and middle side holes of the catheter. Although the authors recognized the value of these multilumen devices, they did advise caution in their use, particularly in the clinical setting with combinations of incompatible drugs. The best approach for prevention of drug-drug incompatibility interactions is to use published information on the physical and chemical properties of medicinal agents which are to be used

concomitantly and avoid their coming into direct contact. The pharmacist is the best health professional to advise on this and the best source of current information is the latest edition of *Martindale, The Extra Pharmacopoeia* (31st edition, 1996).

## ii. DRUG-CONTAINER/PACKAGING INTERACTIONS

It is essential that pharmaceutical containers and packaging should not interact with a drug product and, conversely, that the drug product should not interact with the container or packaging. The two materials which are most widely used as containers and packaging are glass and, more usually, plastics. Incompatibilities between drugs and such materials have been well documented in the literature (D'Arcy, 1983; McElnay *et al.*, 1988; Taormina *et al.*, 1992).

There are a number of mechanisms which are central to drug–container/packaging interactions. These have been described by McElnay and Hughes (1996) as:

- (a) Sorption: a term which describes both adsorption of a drug to a surface and the absorption of a drug into the matrix of the container material.
- (b) Leaching: the process by which components of the container/packaging material migrate into the medicine.
- (c) Permeation: this process involves the transfer of drugs through the container/packaging material to the external surface. This can be followed by evaporation of the drug.
- (d) Polymer modification: some drugs can interact with the polymer and modify its chemical structure; this may lead to changes in its physical properties.

### i. Glass

Glass containers are particularly useful for liquid preparations due to their rigidity, their superior protective qualities and their translucency allowing easy inspection of the contents. Their disadvantages are weight and breakability.

For most drugs' storage, ordinary soda glass or white flint glass containers are used. Amber glass is used for light-sensitive drugs and its composition differs little from white flint glass, except that a small proportion of iron oxide is added under strongly reducing conditions. Although glass is more resistant to chemical attack than other container materials, it is not entirely inert and, when it is in prolonged contact with water, alkali tends to be extracted. Alkaline solutions attack glass more rapidly than water, and the higher the alkali content of the glass the more rapid is this effect. Thus, a glass of low alkali content must be used for containers of preparations liable to attack glass.

Glass completely free from alkali is not practicable but with borosilicate glass, such as Pyrex, the soda content is minimal (about 3.5%), the silica content is around 80% and the boric acid content is approximately 13%. Such glass is inert, neutral and has a very high chemical and thermal resistance. It is, however, hard and more difficult to process than glass with a higher alkali content.

## ii. Plastics

The term plastics covers a wide range of solid composite materials which are usually based upon synthetic resins or upon modified polymers of natural origin and possessing mechanical strength (*Table 9*). The physical, chemical and mechanical properties of plastics' materials are determined by their chemical structure, molecular weight, the alignment of the resin and the type and concentration of additives. Selection of the monomer, for example, ethylene, propylene, glucose, vinyl chloride, determines the chemical structure and the type of substituents in and/or on the polymer chain. Additives include plasticizers added to reduce brittleness, ultraviolet-ray absorbers to prevent degradation by light, and antioxidants and lubricants which are sometimes needed for satisfactory processing. The monomer residues and additives can leach out from the finished plastics materials and have been the main cause of the adverse effects that have been reported.

Knowledge about drug interactions with plastics materials has advanced greatly since the previous edition of this book was published. Information that has so far appeared on the sorption of drugs to intravenous fluid containers, delivery sets, syringes, filters or other plastics apparatus has highlighted that polyvinylchloride (PVC) is the major offender in this respect (Allwood, 1983, 1990; D'Arcy, 1983). Fortunately, in only a few cases, is this sorption phenomenon and loss of drug from fluid likely to present a clinical hazard; in most instances methods are available to prevent or overcome the problem, providing that it is first recognized.

Sorption is probably the most important mechanism for drug interactions with container materials or packaging. Current information suggests that the following drugs may exhibit clinically significant sorption to plastics materials: amiodarone, chlormethiazole, diazepam, glycercyl trinitrate (nitroglycerin), insulin, isosorbide dinitrate, lignocaine, vitamin A acetate, and a miscellaneous group of drugs including hydralazine hydrochloride, some phenothiazines, thiopentone sodium and warfarin sodium. In addition, some drugs alter the physical characteristics of plastics materials, for example, the general anaesthetic gas, cyclopropane, is incompatible with flexible plastics or rubber tubing; methoxyflurane, a volatile anaesthetic, is significantly absorbed by the rubber in anaesthetic circuits and it partially solubilizes PVC plastics. Paraldehyde has long been known to have a solvent action on rubber, it also solubilizes polystyrene and styrene-acrylonitrile copolymer and should therefore not be injected with syringes made with these materials.

Chloroquine binds strongly to soda glass (60–90% bound) and to cellulose acetate filters (58–64% bond) but not seemingly to borosilicate glass or to polycarbonate, polypropylene, or polystyrene containers (Geary *et al.*, 1983; Yahya *et al.*, 1985). These interactions can have serious implications in the laboratory estimation of chloroquine resistance to the malaria parasite.

Kowaluk *et al.* (1981, 1982, 1983) have done much to investigate the extent of drug–container interactions. They examined the stability of 46 injectable drugs stored in PVC bags in the dark for periods of up to 3 months; drugs in glass vials served as controls. Five of the drug products: chlormethiazole edisylate, diazepam, hydralazine hydrochloride, thiopental sodium and warfarin sodium were lost from

Table 9. POLYMER COMPOUNDS WHICH ARE WIDELY USED IN PLASTIC PHARMACEUTICAL PACKAGING AND INTRAVENOUS ADMINISTRATION EQUIPMENT (AFTER YAHYA ET AL., 1986)

Chemical name	Plastic type	Repeating unit of the polymeric structure of the plastic
Cellulose acetate	Amorphous thermoplastic	$  \begin{array}{c}  \text{CH}_2-\text{OR} \\    \\  \text{CH}-\text{O} \\    \quad \diagdown \\  \text{CH}-\text{CH} \\    \quad   \\  \text{RO} \quad \text{OR} \\  \text{R} = \text{H}  \end{array}  \text{CH}-\text{O}-\text{C}-\text{CH}_2-\text{OR}  $
Cellulose propionate	Amorphous thermoplastic	$  \begin{array}{c}  \text{CH}_2-\text{OR} \\    \\  \text{CH}-\text{O} \\    \quad \diagdown \\  \text{CH}-\text{CH} \\    \quad   \\  \text{RO} \quad \text{OR} \\  \text{R} = -\text{CO}-\text{C}_2\text{H}_5  \end{array}  \text{CH}-\text{O}-\text{C}-\text{CH}_2-\text{OR}  $
Ethylvinyl acetate	Amorphous thermoplastic	$  \begin{array}{c}  \text{CH}_2-\text{CH}- \\    \\  \text{O}-\text{CO}-\text{CH}_2-\text{CH}_3  \end{array}  $
Methacrylate butadiene styrene	Amorphous thermoplastic	Co-polymer
Polyethylene	Partially crystalline thermoplastic	$  \begin{array}{c}  \text{CH}_2-\text{CH}_2-  \end{array}  $
Polypropylene	Partially crystalline thermoplastic	$  \begin{array}{c}  \text{CH}_2-\text{CH}- \\    \\  \text{CH}_3  \end{array}  $
Polystyrene	Crystalline thermoplastic	$  \begin{array}{c}  \text{CH}_2-\text{CH}- \\    \\  \text{C}_6\text{H}_5  \end{array}  $
Polyvinylchloride	Amorphous thermoplastic	$  \begin{array}{c}  \text{CH}_2-\text{CH}- \\    \\  \text{Cl}  \end{array}  $

solution to a substantial extent after 1 week. The main physicochemical determinants controlling drug sorption appeared to be the extent of ionization and lipid solubility of the drug.

In other studies, they added 45 drugs to intravenous fluids and drug loss was studied after simulated infusion via plastics infusion sets, with and without burette chambers, glass infusion bottles, polyethylene and silastic tubing with glass syringes on an infusion pump, and all-plastics, single-use syringes. Chlormethiazole edisylate, chlorpromazine hydrochloride, diazepam, promethazine hydrochloride, thiopental sodium, thioridazine hydrochloride, and trifluoperazine were lost from solution during infusion through at least one of the systems. The loss, with most drugs, was slow, time dependent, and concentration dependent which indicated a diffusion-controlled sorption process rather than a binding-absorptive process. Drug loss was lowest in short lengths of small-diameter tubing with low permeability constants. None of the drugs was lost when stored in all-plastics, single-use syringes.

There are two drugs for which sorption is a particular problem, insulin and nitrates. A number of studies have shown the non-specific binding of insulin from dilute solutions. This was first shown by Ferrebee *et al.* (1951) who showed that the drug was strongly absorbed by laboratory glassware. Additional studies showed that insulin also binds to siliconized glassware, paper and polypropylene and to commercial burette intravenous administration sets, especially Sureset (methacrylate butadiene styrene burette and polybutadiene tubing) (see McElnay and Hughes (1996) for references). This non-specific adsorption of insulin, which has been a specific problem in plastic tubing in insulin pumps, can best be prevented by administering the insulin via a small volume syringe via a syringe pump, since the surface area is much reduced compared with the total amount of insulin present.

A number of studies have reported interaction of a range of vasodilator nitrates (e.g. glyceryl trinitrate and isosorbide dinitrate) with packaging and intravenous delivery equipment. A number of mechanisms are involved simultaneously, including adsorption, absorption and permeation. Studies by a number of groups (see McElnay and Hughes (1996) for references) have confirmed that these nitrates are removed from aqueous solutions and from dextrose and/or saline admixtures by plastic materials, especially PVC where losses of up to 70% could be anticipated. Losses with polyethylene did not exceed 15% under similar conditions (Hansen and Spillum, 1991) and the use of Softbag containers (polypropylene-lined infusion bag) did not show any sorption with glyceryl trinitrate, diazepam or warfarin sodium in normal saline (Salomies *et al.*, 1994).

Roberts *et al.* (1991) estimated the time course of the sorption of drugs using a diffusional model in which the plastic was assumed to act as an infinite sink. This model appeared to be suitable for estimation of storage relevant to clinical usage, and enabled the magnitude of the uptake in a specified time to be described by a single parameter known as the sorption number. The sorption number was defined by the plastics-infusion solution partition coefficient, the diffusion coefficient in the plastics material and the exposed surface area of the plastics. This sorption number could be used to predict the effects of a number of factors (e.g. time, plastics surface

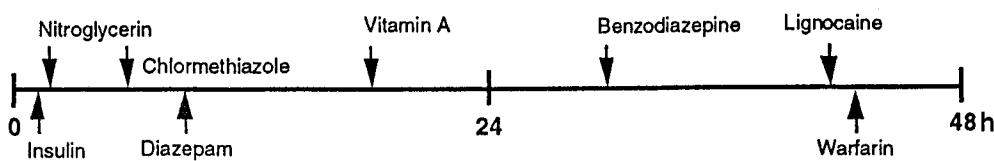


Fig. 9. Time-scale for clinically significant losses of drug due to sorption to plastics materials (Allwood, 1994).

area, solution volume and pH on fractional drug loss. Jenke (1993) developed a similar model in which storage was a critical factor in predicting sorption. At long storage times the infinite sink approach, as defined by Roberts *et al.* (1991), was inaccurate, while at shorter storage times the sorption profile for a solute could be estimated from its hexane–water and octanol–water partition coefficients via a simple diffusion-based expression.

Not all sorption interactions are clinically significant. The schematic representation of an arbitrary time scale cited by McElnay and Hughes (1996) and reproduced in Fig. 9 illustrates that those interactions occurring close to time are clinically significant, whereas those occurring at the other end of the scale may be considered insignificant.

#### *a. Leaching*

Leaching is the migration of substances from container/packaging materials into a medicine. Examples are the leaching of alkali from soda-glass bottle, and the leaching of zinc salts used as activators in rubber closures. Barium ions leached from borosilicate glass may react with the sulphates of drugs such as kanamycin, atropine or magnesium ions to form barium sulphate crystals, the presence of sulphurous acid salts as antioxidants may also result in the formation of crystals in solutions (Lund, 1994). Leaching of plastics components has also received much attention (see McElnay and Hughes, 1996). PVC has been a particular problem, with the plasticizer diethylhexylphthalate (DEHP) leaching from PVC bags induced by various substances including Tween 20, Tween 80, polyoxyethylated castor oil, polysorbate 80, and the vehicles used in paclitaxel and taxotere formulations. Paclitaxel, used in metastatic ovarian cancer, is formulated in 49% dehydrated alcohol and polyoxyethylated castor oil, the latter being known to leach the plasticizer (DEHP) from PVC infusion containers and intravenous administration sets (Pearson and Trissel, 1993). It is therefore recommended that paclitaxel is used with non-PVC containing equipment (ABPI Data Sheet Compendium, 1994–95).

#### *b. Permeation*

Permeation is a combination of absorption followed by migration to the outer surface, from which the drug is released by evaporation. Losses may be substantial and continuous (Allwood, 1994). Permeation may also occur due to passage of gases, vapours and liquids through packaging; water vapour permeates through

silicone rubber and, to varying degrees, through plastics, particularly PVC and polystyrene (Lund, 1994). One of us (PFD'A) observed such a phenomenon with an experimental formulation of semi-solid laxative preparation filled into a plastics tube. The idea was that travellers would find this useful by ingesting a measured length of the extruded material. Unfortunately the purgative formulation permeated the tube and caused a faecal colour staining. The project was dropped.

As has already been mentioned, the loss of glyceryl trinitrate from intravenous fluid containers, particularly PVC, involves a degree of permeation through plastics materials followed by a loss of evaporation. It was also common at one time to provide an outer plastics envelope for plastic infusion bags; this reduced permeation of the fluids.

#### c. *Polymer Modification*

Kowaluk *et al.* (1981) reported that PVC infusion bags containing chlormethiazole became more pliable and softer on storage, particularly with high concentrations of the drug. Both sorption and permeation was enhanced. It has been suggested that this was due to greater PVC polymer chain flexibility through plasticization.

### DRUG INTERACTION WITH CONTACT LENSES

A number of drugs can enter into surface interaction with plastics contact lenses. For example, a permanent and damaging colouration of contact lenses has been reported with the use of rifampicin (Lyons, 1979), and this is not entirely surprising since this antibiotic is known to cause reddish discolouration of tears, urine and sputum. It has also long been known that fluorescine stains soft lenses and may permanently spoil them. Rose Bengal is also contraindicated, although the concentrated dye may be removed from the lens material by repeated leaching processes. Adrenochrome pigmentation associated with the use of adrenaline eye drops has been reported to cause a dense brown colouration of the lens (Sugar, 1974). Sulphasalazine used in the treatment of colitis has been implicated in the yellow staining of soft contact lenses (Riley *et al.*, 1986). It is now commonplace for those patients undergoing topical treatment with eye drops and who also wear insertable lenses to be advised to remove their lenses for the duration of the treatment. It is more difficult, however, to predict possible interactions in those patients undergoing systemic therapy, and it is only through isolated reports in the literature that patients can be warned of this possibility. Generally, little predictive work has been done on this type of interaction.

### DRUG-EXCIPIENT INTERACTIONS

A number of drug-excipient interactions are listed in The British Pharmaceutical Codex (Lund, 1994). Interactions between cationic and anionic agents may be particularly troublesome. For example, carmellose sodium, an anionic polymer,

precipitates large cations such as neomycin and chlorpromazine in solution. Benzalkonium chloride and other cationic antimicrobials are inactivated to a varying degree in the presence of carbomer (carboxypolyethylene) and other anionic polymers. The formation of complexes between drug and excipient may also be common. Phenolic preservatives may be partly inactivated in complexes formed with macrogol derivatives. The non-ionic povidone may complex with anionic or cationic dyes, and drugs such as chlorpromazine and chloramphenicol and gels made with povidone may increase in viscosity by complexing with 8-hydroxyquinoline sulphate or thiomersal sodium.

Excipients may also affect the stability of a drug leading to reduced bioavailability and reduced therapeutic efficacy, for example sodium metabisulphite rapidly inactivates cisplatin and propylene glycol, and macrogols catalyse the degradation of benzoyl peroxide to benzoic acid and carbon dioxide. There are many such reports and two recent examples are: the incompatibility of pyridoxine hydrochloride (vitamin B<sub>6</sub>) with mannitol, lactose and corn starch (Durig and Fassihi, 1993), and the adverse effects of cellulose derivatives (methylcellulose and sodium carboxy methylcellulose) on the stability and bioavailability of the anorectic, diethylpropion (Gomez *et al.*, 1993). Other examples of drug-excipient interactions have been given by McElnay and Hughes (1996), while the 2nd edition of the *Handbook of Pharmaceutical Excipients* (Wade and Weller, 1994) lists incompatibilities in the majority of its monographs. All of these serve to illustrate that no component of any formulation can be regarded as inactive. D'Arcy (1990) has discussed adverse reactions to excipients in pharmaceutical formulations and has classified such excipients into classes and categories.

## 7. AGE AND GENETIC FACTORS

### 1. AGE

It has long been known that specific patient factors can influence the course of therapy and the adverse drug reactions and interactions that may follow (Wallace and Watanabe, 1977; Ouslander, 1981; Braverman, 1982; Greenblatt *et al.*, 1982; Shaw, 1982; D'Arcy and McElnay, 1983; Royal College of Physicians, 1984; Nolan and O'Malley, 1988a,b; Denham, 1990; Williams and Lowenthal, 1992; McElnay and D'Arcy, 1996). Of these factors, age and genetic influences have been pinpointed as significant contributors to problems with drug therapy.

It has long been established that elderly patients use more medicines than younger age groups (Landahl, 1987; Sloan, 1992; Williams and Lowenthal, 1992; Stewart and Cooper, 1994) and thus have a greater risk of experiencing a drug-drug interaction (Kellaway and McCrae, 1973; Lawson and Jick, 1976; Levy *et al.*, 1980; Williamson and Chopin, 1980; Simons *et al.*, 1992; Schenker and Bay, 1994; Stanton *et al.*, 1994; Stewart and Cooper, 1994). It must be understood, however, that there is virtually no direct evidence in the literature that age *per se* can cause drug-drug interactions. Its role is more in enhancing the effects of such interactions when they occur. Age thus tends to exert a quantitative influence on the interaction but does not alter its qualitative spectrum.

Senescence is frequently evoked to explain the unwanted sequelae to therapy, undoubtedly rightly, providing senescence is regarded as being accompanied, for example, by physiological changes due to age (Lamy, 1991), by small body mass, poor renal function and impaired function of other organs, notably the liver. *Table 10* shows some of the key changes that occur as a result of physiological ageing. In elderly patients the reserve capacity of many organs may be considerably reduced, and because of this erosion there is a narrowing of the safety margin between the therapeutic and toxic dose of many drugs. As a result of this the elderly, as a group, get rather more than their fair share of drug-induced disease and the complications of drug-drug interactions.

*Table 11* shows, as an example, the drug-drug interactions identified by Gosney and Tallis (1984) in their survey of interacting drugs in elderly patients admitted to hospital. Although none of these combinations were potentially life-threatening, 51 combinations were likely to lead to potentially serious side effects, and 27 were significant in as much as they could lead to suboptimal treatment.

There are many striking examples of age-related alterations of both kinetics and dynamics of drugs. Every drug used in the elderly should have its pharmacology

## 54 A MANUAL OF ADVERSE DRUG INTERACTIONS

*Table 10. SOME KEY CHANGES AS A RESULT OF PHYSIOLOGICAL AGEING\**

System	Key changes
Cardiovascular system	Decrease in cardiac output Decrease in stroke volume Loss of elasticity of blood vessels Decrease in recovery rate to restore basal heart rate following exercise Pre-disposition to blood hypercoagulability Decrease in deposition of fibrin in blood vessel walls Decrease in peripheral perfusion Decrease in organ blood flow
Central nervous system	Changes in receptor and target organ sensitivity Decrease in cerebral perfusion Slowing of cerebral processes
Respiratory system	Decrease in the elasticity of lung tissue Lessening of ciliary activity Decrease in dead space in lungs Decrease in forced expiratory volume Decrease in peak flow Wasting of muscles in diaphragm
Endocrine system	Decrease in glucose tolerance Decrease in peripheral responsiveness to insulin Decrease in thyroid functional activity but increased tissue sensitivity to thyroid hormones Decrease in normal thyroxine turnover Reduction of plasma binding of thyroid hormones Decrease in basal adrenal activity Reduction of estrogen level Decrease in the production of progesterone after menopause Decrease in free androgens in men Altered hormonal control of bone homeostasis Compromized immunological systems
Gastrointestinal systems	Decrease in acid secretion Decrease in gastric emptying rate Decrease in gut motility Decrease in peristaltic activity Decrease in gastric blood flow Decrease in absorption of calcium and iron from small intestine
Hepatic system	Reduction in hepatic blood flow Decreased metabolic capacity
Genito-urinary system: Kidney	Decrease in glomerular filtration rate Decrease in functioning renal glomeruli Decrease in renal blood flow Decrease in excretory and reabsorptive capacities of renal tubules
Bladder	Loss of supporting elastic tissue Detrusor muscle hypertrophy
Reproductive tract	Decrease in vaginal secretions Increase in pH of vaginal secretions

\*Source: Collier *et al.* (1993).

Table 11. DRUG INTERACTIONS\*

<i>Drug(s)</i>		<i>Nature of clinically most important interaction</i>	<i>Comment</i>	<i>No. cases</i>
Frusemide	Aminoglycosides	Increased ototoxicity and nephrotoxicity	Potentially serious. Probably avoidable	24
Frusemide	Cephalosporins	Increased nephrotoxicity	Potentially serious. Probably avoidable	9
Warfarin	Phenylbutazone	Increased risk of haemorrhage	Potentially dangerous. Avoidable	1
Warfarin	Aspirin	Increased risk of haemorrhage	Potentially dangerous. Avoidable	3
Heparin	Aspirin	Increased risk of haemorrhage	Potentially dangerous. Avoidable	1
Verapamil	Propranolol (within 6 h)	Risk of asystole	Potentially dangerous. Avoidability uncertain	2
Frusemide	Prednisolone (with potassium supplementation)	Antagonism	Significant interaction. Avoidability uncertain	16
Frusemide	Prednisolone (without potassium supplementation)	Increased risk of potassium loss as well as antagonism (4 of these had $K^+ < 2.8 \text{ mmol/l}$ )	Potentially serious. Risk could have been reduced by potassium supplementation	14
Loop diuretics	Indomethacin	Antagonizes diuretic effect	Possibly serious. Could have been avoided by using alternative analgesic	4
Loop diuretics	Other non-steroidal anti-inflammatory drugs	May antagonize diuretic effect	Possibly significant. Avoidability uncertain	15
Carbenoxolone	Spironolactone	Inhibition of ulcer healing. Interference with treatment of cardiac failure	Potentially significant. Should have been avoided	1
Phenylbutazone	Chlorpromazine	Increased risk of leucopenia	Potentially dangerous. Avoidable	2
Iron	Antacid	Interference with action/absorption	Possibly significant. Avoidable	2
Cimetidine	Antacid	Interference with action/absorption	Possibly significant. Avoidable	20
Digoxin	Antacid	Interference with action/absorption	Possibly significant. Avoidable	5
Tetracycline	Antacid	Interference with action/absorption	Significant. Avoidable	3
Tetracycline	Iron	Interference with action/absorption	Significant. Avoidable	2
Warfarin	Co-trimoxazole	Interference with control. Increased risk of bleeding	Significant. Could have been avoided by using trimethoprim alone	5
Phenytoin	Co-trimoxazole	Potentiation	Possibly significant. Could have been avoided by using trimethoprim alone	1
Phenylbutazone	Thyroxine	Interference with thyroid function test	Possibly significant. Avoidable	1
Tolbutamide	Co-trimoxazole	Potentiation	Possibly significant. Could have been avoided by using trimethoprim alone	2
		Total		133

\*Source: Gosney and Tallis (1984).

and toxicology specially evaluated in the elderly, yet few elderly patients, if any, participate in clinical trials on new drug substances. One does not question that it is desirable, but it must be appreciated that the ethical situation is not at all clear.

Pharmacokinetic effects of medication may be increased or decreased in the elderly patient. Posner and Rolan (1994) have categorized age-related differences in kinetics between the elderly and young as being primarily due to diminished renal function, altered proportions of body fat and water, reduced cardiac output and some degree of altered hepatic metabolism. Ritschel (1980) has listed some of the changes of drug parameters in the aged, these are given in *Table 12*, while Greenblatt *et al.* (1982) have summarized the relation of age to the clearance of drugs by hepatic biotransformation (*Table 13*).

Pharmacodynamic interactions between drugs produce similar or antagonistic pharmacological effects or side effects. These interactions can be influenced by age as illustrated in the following examples:

The elderly show an increased response to angiotensin-converting enzyme (ACE) inhibitors; they show a reduced responsiveness to propranolol. Data are conflicting for calcium antagonists. The inotropic effect of theophylline is increased with age, but its bronchodilator effect is reduced. The anticoagulant effect of warfarin is increased in elderly patients due to greater fragility of the hepatic synthesis of clotting factors (Shephard *et al.*, 1977). This latter increase is important because warfarin is a drug which is notorious for its involvement in drug interactions and therefore this increased warfarin sensitivity could predispose the elderly patient to greater adverse sequelae should an interaction take place.

Feely and Coakley (1990) emphasized in their review on altered pharmacodynamics in the elderly that the importance of age-related changes in drug sensitivity is being increasingly appreciated. The type, intensity and duration of drug action can be affected, ranging from therapeutic failure to major drug toxicity.

McElnay and D'Arcy (1996) have listed other examples of the pharmacodynamics of drugs being altered in the elderly patient. Alterations in physiological and homeostatic systems including the autonomic nervous system, baroreceptors, thermoregulation and balance have been described. Phenothiazines, diuretics, antihypertensives,  $\beta$ -adrenoceptor antagonists, antidepressants, NSAID, benzodiazepine and lignocaine are all examples of drugs that are likely to produce enhanced pharmacological or toxic effects in the elderly.

The sequelae of interactions involving these drugs or systems will be qualitatively similar in the different age groups but will be more pronounced in their effects on the elderly. Many adverse effects of drugs or drug combinations that may simply be a nuisance to younger patients are much more intensified in the elderly due, for example, to their decreased resistance to the adverse consequences. Indeed, the adverse effects of drug treatments may convert the elderly patient from a sentient human being into a chair-fast incontinent wreck.

A number of investigators have shown that age is not an independent risk factor for drug interactions (Nolan and O'Malley, 1989; Carbonin *et al.*, 1991; Gurwitz and Avorn, 1991; Chrischilles *et al.*, 1992). However, regardless of whether the

Table 12. CHANGE OF DRUG PARAMETERS IN THE AGED\*

<i>Drug</i>	<i>Biological half-life</i>	<i>Volume of distribution</i>	<i>Total clearance</i>
Acetaminophen (paracetamol)	↑	U	↓
Acetanilide	↑	↓	U
Aminopyrine	↑	NI	NI
Amitriptyline	↑	↓	↓
Amobarbital	↑	U	↓
Ampicillin	↑	U	↓
Antipyrine (phenazone)	↑	↓	↓
Aspirin	NI	↑	↓
Carbenicillin	↑	↑	NI
Carbenoxolone	↑	↓	↓
Cefamandole	↑	↑	U
Cefazoline	↑	U	↓
Cefradin	↑	U	↓
Chlordiazepoxide	↑	↑	↓
Chlormethiazole	↑	↑	↓
Chlorthalidone	↑	U	↓
Cimetidine	↑	↓	NI
Cyclophosphamide	↑	↑	NI
Desipramine	↑	NI	NI
Desmethyl diazepam	↑	↑	↓
Diazepam	↑	↑	U or ↓
Digoxin	↑	↓	↓
Dihydrostreptomycin	↑	NI	NI
Doxycycline	↑	U	↓
Flurbiprofen	U	U	U
Gentamicin	↑	↓	↓
Imipramine	↑	NI	NI
Indomethacin	↑	NI	NI
Indoprofen	U	U	U
Kanamycin	↑	NI	↓
Levomepromazine	↑	U	↓
Lidocaine (lignocaine)	↑	↑	U
Lithium	NI	NI	↓
Lorazepam	U or ↑	↓	U or ↓
Methotrexate	↑	↓	↓
Metoprolol	↑	NI	NI
Morphine	↑	NI	NI
Netilmicin	↑	U	↓
Nitrazepam	↑	U	U
Nortriptyline	↑	↓	↓
Oxazepam	↑	↑	NI
Penicillin G	↑	NI	NI
Phenobarbital	↑	NI	NI
Phenylbutazone	↑	U	↓
Phenytoin	NI	NI	↑
Procaine penicillin	↑	NI	NI
Practolol	↑	↓	NI
Propicillin	↑	↓	NI
Propranolol	↑	↓	↓
Protriptyline	↑	↓	↓
Quinidine	↑	↓	↓
Spirostanolactone	↑	NI	NI
Sulbenicillin	↑	↑	NI
Sulfamethizole (sulphasomidine)	↑	U or ↓	↓
Tetracycline	↑	NI	NI

Table 12. CONTINUED

Drug	Biological half-life	Volume of distribution	Total clearance
Theophylline	↑	U or ↓	↓
Thioridazine	↑	NI	NI
Tobramycin	↑	↓	↓
Tolbutamide	↑	↓	↓
Warfarin	↑	U	↓

\*Source: Ritschel (1980).

Table 13. STUDIES ON THE RELATION OF AGE TO THE CLEARANCE OF DRUGS BY HEPATIC BIOTRANSFORMATION\*

Drug or metabolite	Initial pathway of biotransformation <sup>a</sup>
<i>Evidence suggests age-related reduction in clearance</i>	
<i>Small or negligible age-related change in clearance</i>	
Antipyrine <sup>b</sup> (phenazone)	Oxidation (OH, DA)
Diazepam <sup>b</sup>	Oxidation (DA)
Chlordiazepoxide	Oxidation (DA)
Desmethyldiazepam <sup>b</sup>	Oxidation (OH)
Desalkylflurazepam <sup>b</sup>	Oxidation (OH)
Clobazam <sup>b</sup>	Oxidation (DA)
Alprazolam <sup>b</sup>	Oxidation (OH)
Quinidine <sup>b</sup>	Oxidation (OH)
Theophylline	Oxidation
Propranolol	Oxidation (OH)
Nortriptyline	Oxidation (H)
<i>Data conflicting or not definitive</i>	
Meperidine (pethidine)	Oxidation (DA)
Phenylbutazone	Oxidation (OH)
Phenytoin	Oxidation (OH)
Imipramine	Oxidation (OH, DA)
Amitriptyline	Oxidation (OH, DA)
Acetaminophen (paracetamol)	Glucuronidation, sulfation
Amobarbital	Oxidation (OH)

\*Source: Greenblatt *et al.* (1982).

<sup>a</sup>OH denotes hydroxylation and DA dealkylation.

<sup>b</sup>Evidence suggests that the age-related reduction in clearance is greater in men than in women.

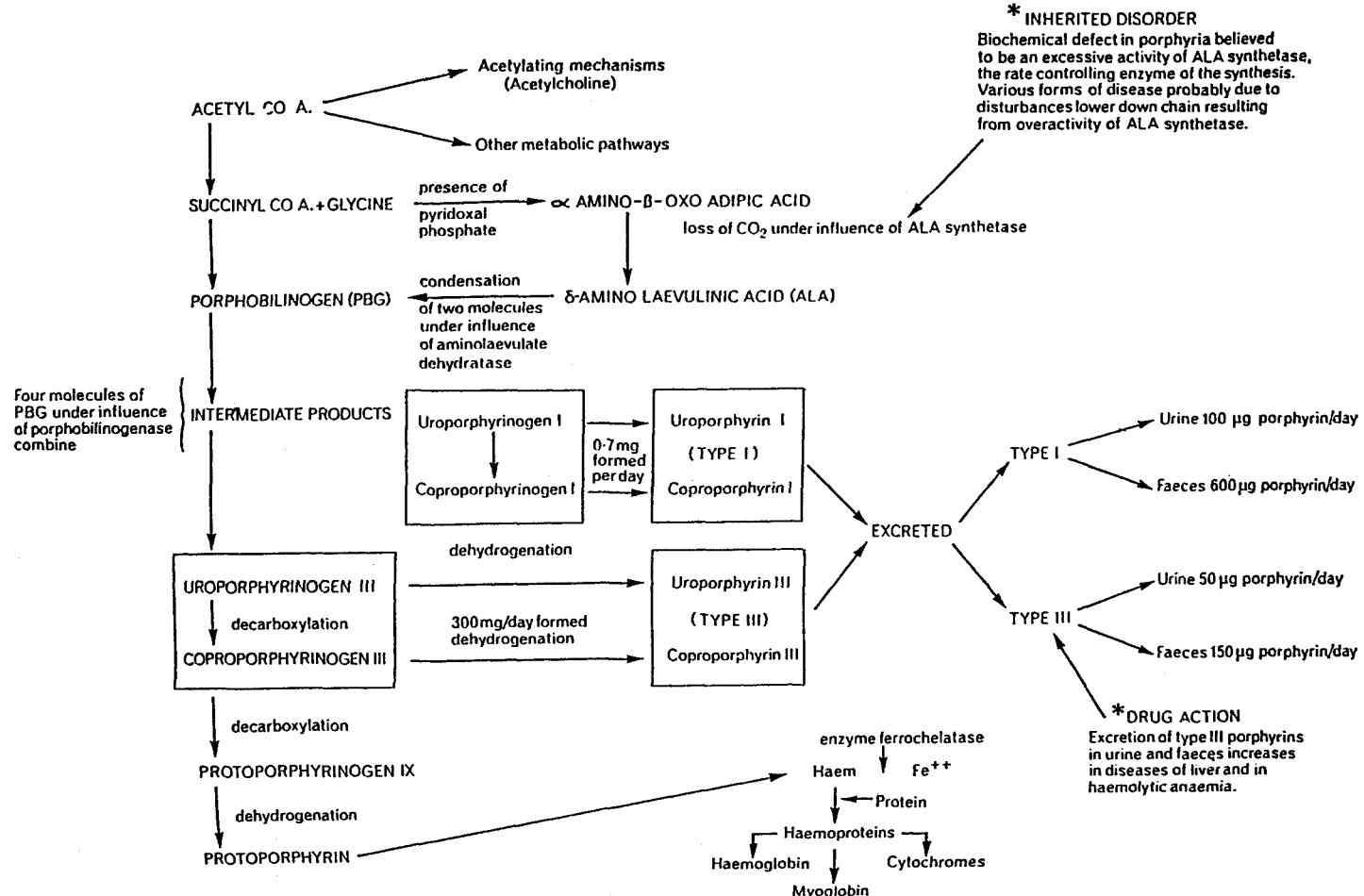


Fig. 10. Overall scheme of porphyrin synthesis (source: Fletcher and Griffin, 1986).

Table 14. DRUGS CLASSIFIED AS TO THEIR ASSOCIATION WITH PORPHYRIA\*

Potentially porphyrogenic drugs	Drugs believed not to precipitate porphyria
Alcohol	Acetazolamide
Alphaxalone	Adrenaline
Aluminium	Alclofenac
2 allyloxy-3 methylbenzamide	<i>Amitriptyline</i>
Amidopyrine (A)	Aspirin
Aminoglutethimide	Atropine
Amitriptyline	
Amphetamines	B vitamins (except pyridoxine)
Androgens (A, C)	Bethanidine
Apronalide	Biguanides
Azapyrazone	Bromides
Azapropazone	Bumetanide
Barbiturates (A, C)	Bupivacaine
Bemegride	Buprenorphine
Busulphan	
Carbromal	Cephalexin
Carbamazepine	Cephalosporins
Chlorambucil	Chloral hydrate
Chloramphenicol	<i>Chloramphenicol</i>
Chlordiazepoxide (A)	Chlormethiazole
Chlormezanone	Chlorpheniramine
Chloroform	Chlorpromazine
Chloroquine (C)	<i>Chloroquine</i>
Chlormethiazole	Chlorthiazides
Chlorpropamide (A, C)	Clobazam
Cimetidine	Clofibrate
Clonazepam	<i>Clonazepam</i>
Clonidine	Codeine
Cocaine	Colchicine
Colistin	Corticosteroids
Cyclophosphamide	Cyclizine
Danazol	Cyclopropane
Dapsone	
Diazepam	Dexamethazone
Dichloralphenazone (A)	Diamorphine
Diclofenac	<i>Diazepam</i>
Diethylhexyl phthalate	Diazoxide
Diethylpropion	Digitalis compounds
Dimenhydrinate	Diphenhydramine
Enflurane	Dicoumarol anticoagulants
Ergot preparations	Disopyramide
Erythromycin	Domperidone
Ethchlorvynol	Droperidol
Ethinamate	
Ethosuximide	EDTA
Etomidate	Ether (diethyl)
Eucalyptol	
Flufenamic acid	Fentanyl
Flunitrazepam	Flurbiprofen
Fluroxine	Fusidic acid
Frusemide	
	Gentamicin
	Glipizide
	Guanethidine
	Heparin

Table 14. CONTINUED

Potentially porphyrogenic drugs	Drugs believed not to precipitate porphyria
Glutethimide	<i>Hydralazine</i>
Gold preparations	Hyoscine
Griseofulvin (A)	
Halothane	Ibuprofen
Hydantoins (phenytoin, ethotoin, mephentoin)	<i>Imipramine</i>
Hydralazine	<i>Indomethacin</i>
Hydrochlorthiazide	Insulin
Hyoscine N-butyl bromide	Ketamine
	Ketoprofen
Imipramine	Labetolol
Indomethacin	Lithium
Isoniazid	Lorazepam
Isopropylmeprobamate	Mandelamine
Lignocaine	Mecamylamine
Mefenamic acid	Meclozine
Mephenazine	<i>Mefenamic acid</i>
Meprobamate	Mersalyl
Mercury compounds	Metformin
Methoxyflurane	Methadone
Methsuximide	Methenamine mandelate
Methyldopa	Methylphenidate
Methyprylon	Morphine
Metoclopramide	Naproxen
Metyrapone	Neostigmine
Metronidazole	<i>Nitrofurantoin</i>
Nalidixic acid	Nitrous oxide
Nikethamide	Nortriptyline
Novobiocin	
Nitrazepam	<i>Oxazepam</i>
Nitrofurantoin	Oxpentifylline
Oral contraceptives	Paracetamol
Oxazolidinediones (paramethadione and trimethadione)	<i>Paraldehyde</i>
Oestrogens (A, C)	Penicillamine
Oxazepam	Penicillins
Pancuronium	<i>Pethidine</i>
Paraaldehyde	Phenformin
Pargyline	Pheniramine
Pentazocine	Phenothiazines (e.g. chlorpromazine)
Pentylenetetrazol	Phenoperidine
Pethidine	<i>Phenylbutazone</i>
Phenazone	Prednisolone
Phenelzine	Procaine
Phenoxybenzamine	Prilocaine
Phensuximide	Promethazine
Phenylbutazone	Propantheline bromide
Phenylhydrazine	<i>Propanidid</i>
Primidone	Primaquine
Probenecid	Propoxyphene
	Propranolol
	Prostigmine

Table 14. CONTINUED

<i>Potentially porphyrogenic drugs</i>	<i>Drugs believed not to precipitate porphyria</i>
Progestogens (A, C)	<i>Pyrimethamine</i>
Propanidid	
Pyrazinamide	<i>Quinine</i>
Pyrazolones (antipyrine, isopropylantipyrine, dipyrone sodium phenyl dimethyl pyrazolone)	<i>Reserpine</i> <i>Resorcinol</i> <i>Rifampicin</i>
Pyridoxine	
Pyrimethamine	<i>Streptomycin</i> <i>Succinylcholine</i>
Ranitidine	
Rifampicin	<i>Tetracyclines</i> <i>Tetraethylammonium</i> <i>bromide</i>
Sodium valproate	
Spironolactone	<i>Thiouracils</i>
Steroids	<i>Tricyclic antidepressants</i> (amitriptyline)
Streptomycin	<i>Trifluoperazine</i>
Succinimides (ethosuximide, methsuximide, phensuximide)	<i>Thiazides</i>
Sulphonal	<i>Tripeptenamine</i>
Sulphonamides (A)	<i>Tubocurarine</i>
Sulphonylureas	
Sulthiame	<i>Sodium valproate</i>
Tetracyclines	Vitamin C
Theophylline	
Tolazamide	
Tolbutamide (A, C)	
Tranycypromine	
Trional	
Troxidone	
Valproic acid	
Viloxazine	
Xylocaine	

A, acute porphyria; C, cutaneous porphyria.

Substances marked in italics have been variously described as causing porphyria or being safe to administer to patients with porphyria (see text).

\*Source: Fletcher and Griffin (1986).

elderly are more sensitive to the adverse effects of medication, they have more disease, consume more medicines and are over-represented in nearly every study of adverse drug reactions (Schneider *et al.*, 1992).

## GENETIC FACTORS

The term 'pharmacogenetic disorder' was originally coined by Vogel (1959) and was originally limited to hereditary disorders revealed solely by the use of drugs. Its meaning has now been enlarged to embrace all genetic contributions to the considerable variation that exists in the interaction between the human or animal subject and the pharmacological agents that are administered. The term can there-

Table 15. DRUGS REPORTED TO INDUCE HAEMOLYSIS IN SUBJECTS WITH G6PD DEFICIENCY

Drug	<i>Haemolysis</i>	
	<i>Black subjects</i>	<i>Caucasian subjects</i>
Acetanilide	+++++	
Dapsone	++	+++
Furazolidone	++	
Nitrofural	++++	
Nitrofurantoin	++	++
Sulphanilamide	+++	
Sulphapyridine	+++	+++
Sulphacetamide	++	
Salazosulphapyridine	+++	
Sulphamethoxypyridazine	++	
Thiazosulphone	++	
Quinidine		++
Primaquine	+++	+++
Pamaquine	++++	
Pentaquine	+++	
Quinocide	+++	++
Naphthalene	+++	+++
Neoarsphenamine	++	
Phenylhydrazine	+++	
Toluidine blue	++++	
Trinitrotoluene		+++

Table 16. ADVERSE REACTIONS DUE TO POOR MICROSOMAL OXIDATION\*

<i>Adverse reaction</i>	<i>Drugs concerned</i>
Lactic acidosis	Metformin
Agranulocytosis	Carbamazole Phenylbutazone Chlorpromazine Nortriptyline Imipramine Thioridazine Captopril
Neuropathy or sensory disturbances	Phenytoin
Hepatic adenoma	Oral contraceptives
Cerebellar signs	Phenytoin
Vitamin D-deficiency-like state	Phenytoin Phenobarbitone
Folate deficiency-like state	Phenytoin Phenobarbitone
Syncope	Prazosin
Malignant ventricular arrhythmias	Mexiletine Disopyramide
Bradycardia	Propranolol Metoprolol

\*Source: Smith and Shah (1984, personal communication) and Smith and Idle (1981).

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## **8. HERBAL AND OTHER NON-ORTHODOX REMEDIES**

Medicines derived from plants formed the majority of the earlier *materia medica* because chemically synthesized compounds were then not available. Many of these herbs have stood the test of time and critical clinical assessment and have found their way into the pharmacopoeias of orthodox medicines sometimes as the isolated and chemically standardized active ingredient. Such drugs as cocaine, colchicine, coumarin anticoagulants, digoxin, ephedrine, morphine, quinine and quinidine, reserpine, tubocurarine, sennosides and the ergot and vinca alkaloids entered orthodox medicinal use by this route. (De Smet and D'Arcy, 1996).

There are many types of herbal remedies (*Table 17*). At one end of the scale there are the self-made teas prepared from self-collected herbs. At the other end there are officially registered drug products which have passed through a rigid registration procedure. In between there are a bewildering range of nostrums that have obscure origins and even more obscure constituents. The latter classes may be a mixture of herbal products with other ingredients of non-herbal origin (e.g. arsenic or lead) or undeclared Western drugs (e.g. corticosteroids, non-steroidal anti-inflammatory/antirheumatic agents (NSAIDs), or paracetamol). Although herbal medicines are by far the largest component of non-orthodox remedies, they do not have exclusive claims. Other non-orthodox remedies range from preparations of animal origin, minerals, vitamins and amino acids; many of which are capable of interfering with orthodox medicines.

A survey by Wharton and Lewith (1986) showed that only 5% of British doctors claimed more than a poor knowledge of herbal medicines. Medical practitioners generally believed that herbal preparations were residues from the remote past, that they were harmless and largely ineffective. Many patients believed that they were safe, simply because they were natural products, and that they were often miraculously effective. Unfortunately both patients and doctors are misinformed since many herbal products can be exceedingly toxic and may indeed present peculiar hazard if taken in combination with orthodox medicines. A special section has been given to this topic in the Tables of Drug Interactions that appear in Part 2 of this book. More detailed information of the nature and mechanisms of these interactions has been given in a series of reviews by D'Arcy (1991, 1993), De Smet (1992a,b), De Smet and D'Arcy (1996) and books by De Smet *et al.* (1992, 1993).

Some of these interactions are based upon a firm pharmacological basis (*Table 18*), but often their clinical relevance still needs to be established. Others have been presented in anecdotal reports with lack of data essential to establish a firm cause-effect relationship. It is necessary to emphasize this if warnings are to be given

*Table 17. DIFFERENT TYPES OF HERBAL REMEDIES\**

Raw materials for self-preparation
By self-collection
Through commercial channels
(Semi) finished non-medicinal products
Dietary supplements
Health foods
Recreational herbs, etc
Registered medicines
By special procedure
By regular procedure

\*Source: De Smet and D'Arcy (1996).

*Table 18. HERBAL DRUGS WITH WELL-KNOWN CONSTITUENTS AND THEIR INTERACTIONS\**

<i>Herbal drug</i>	<i>Interactions</i>
<i>Adonis vernalis</i>	
<i>Convallaria majalis</i>	Due to the presence of cardioactive glycosides, digitalis-like effects and potentiation of toxicity are possible.
<i>Digitalis</i> species	
<i>Nerium oleander</i>	
<i>Strophanthus</i> species	Although <i>Crataegus</i> extracts do not contain digitalis-like glycosides, potentiation of digitalis activity has been reported to occur in guinea pigs. The evidence from this study has been challenged.
<i>Urginea maritima</i>	
<i>Xsymalobium undulatum</i>	
<i>Atropa belladonna</i>	
<i>Datura stramonium</i>	All these plants contain anticholinergic tropane alkaloids such as hyoscyamine and/or scopolamine which can potentiate the effects of synthetic drugs with similar pharmacological activity (e.g. antidepressants, antihistamines, antispasmodics).
<i>Hyoscyamus niger</i>	
<i>Mandragora officinarum</i>	
<i>Scopolia carniolica</i>	
<i>Ephedra</i> species	The tertiary alkaloid epedrine could interfere with conventional antihypertensive therapy.
<i>Papaver somniferum</i>	The opium alkaloids of the oriental poppy will interact with and potentiate the effects of analgesics and other CNS depressants.
<i>Pilocarpus pennatifolius</i>	The alkaoid pilocarpine has potent cholinergic effects which may antagonize orthodox treatment with anti-asthma and anticholinergic agents.
<i>Rauwolfia serpentina</i>	The reserpine-rescinnamide alkaloids of this root will interact and potentiate the effects of antihypertensives, psychotropics and CNS depressants.

\*Source: De Smet and D'Arcy (1996).

about likely interactions since the sparse reports of drug interactions between non-orthodox products and Western medicines neither confirms their safety in use nor indeed suggest that the incidence of interactions is small. The simple fact is that most interactions of this type will not be recognized as such by the self-medicated patient and will not be reported to an orthodox medical practitioner and therefore will not appear in the medical or pharmaceutical literature. In many of the cases where herbal products have been associated with actual human poisoning, analysis

has shown that this was not in fact caused by the herbs alleged to be in the product, but resulted from substitution or contamination of the declared ingredients, intentionally or by accident, with a more toxic botanical, a poisonous metal, or a potent non-herbal drug substance (De Smet, 1992a).

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## 9. INTERFERENCE WITH LABORATORY TESTING

Laboratory tests, physical examination and the patients medical history often provide the main key to accurate diagnosis and to subsequent rational therapy. One of these key features — laboratory tests — can be influenced in sensitivity or specificity (or both) by the drugs consumed by the patient. Frequently the influence of medication on the reliability of subsequent laboratory tests is not realized or merely overlooked. The mechanisms of such interactions can be generally classified into two areas: pharmacological and methodological interferences. Whenever a drug-laboratory test interaction is established it should be communicated to the medical community so that they may avoid possible errors in diagnosis.

Many factors can cause a laboratory error or false-positive results. They include human error, equipment error, environmental changes, chemicals added to specimens and the presence of endogenous substances. Another important factor which has an effect is the presence of medications in the body fluid tested or influencing the functions of the body. This last factor, medication, is often overlooked. This topic of interactions involving laboratory tests has not been covered specifically in this volume, however, an excellent and authoritative review has recently been written by Yosselson-Superstine (1996) while other compilations of published studies have been prepared by Salway (1990) and Young (1990).

In general, such interference can be classified into two major types: (1) pharmacological interferences, also known as biological or *in vivo* interferences, and (2) methodological interferences also known as analytical or *in vitro* interferences. Pharmacological interferences are by far the most frequent type. They affect the result of the tests by virtue of the activity of the drug or its metabolites in the body, regardless of the method employed in the test. This is easy to detect when the change in the test value is expected, but it is more difficult to interpret when it is an unexpected toxicological effect of the drug.

A simple example to illustrate this type of interference is in tests that measure the glycaemic control of diabetic patients. Thiazide diuretics can elevate blood sugar levels from weeks to years after therapy is started (Joseph and Schuna, 1990) and this can seriously affect the blood sugar levels of some patients taking, for example, sulphonylurea hypoglycaemics. The mechanism involved in this interference could be due to the hypokalaemia induced by the diuretic or even to the possible inhibition of insulin secretion from the pancreatic  $\beta$ -cells.

An example of methodological interference is that with colour. Most of the laboratory tests in chemical pathology have a colourimetric component which can be subject to the effect of foreign chromagens. Creatinine measurement is one of

**Table 19.** DRUGS WHICH MAY DISCOLOUR URINE\*

<i>Drug/drug class</i>	<i>Colour produced</i>
Acetanilide	Yellow to red
Aloe	Yellow-pink to red-brown in alkaline urine
Aminopyrine	Red
Aminosalicylic acid	Discolouration red in hypochlorite solution
Amitriptyline	Blue-green
Anisindione	Pink or red to red brown in acidic urine, orange in alkaline urine
Antipyrine	Red-brown
Azuresin	Blue or green
Cascara	Yellow-brown in acidic urine, yellow-pink in alkaline urine, turning black on standing
Chloroquine	Rust yellow to brown
Chlorzoxazone	Orange or purplish red
Cimetidine (injection)	Green
Danthon	Pink to red or red-brown in alkaline urine
Daunorubicin	Red
Deferoxamine mesylate	Reddish
Dimethylsulfoxide (DMSO)	Reddish due to haemoglobinuria
Diphadione	Orange in alkaline urine
Doxorubicin	Red
Emodin	Pink to red or red-brown in alkaline urine
Ethoxazena	Orange to orange-brown
Ferrous salts	Black
Furazolidone	Rust yellow to brown
Idarubicin	Red
Indigotindisulfonate	Blue or green
Indomethacin	Green due to biliverdinaemia
Iron sorbitex	Black
Levodopa	Dark on standing in hypochlorite solution
Methocarbamol	Dark to brown, black-green on standing
Methyldopa	Dark on standing in hypochlorite solution
Methylene blue	Blue or green
Metronidazole	Dark
Mitoxantrone	Dark blue or green
Nitrofurantoin	Rust yellow to brown
Pamaquine	Rust yellow to brown
Phenacetin	Dark brown to black on standing
Phenazopyridine	Orange to orange-red
Phenindione	Orange-red in alkaline urine
Phenolphthalein	Pink to purplish-red in alkaline urine
Phenolsulphonphthalein (PSP)	Pink to red in alkaline urine
Phenothiazines	Pink to red or red-brown
Phensuximide	Pink to red or red-brown
Phenytoin	Pink to red or red-brown
Primaquine	Rust yellow to brown
Promethazine (injection)	Green
Propofol (injection)	Green
Quinacrine	Deep yellow in acidic urine
Quinine	Brown to black
Resorcinol	Dark green
Riboflavin	Yellow fluorescence
Rifampicin	Bright red-orange
Santonin	Yellow in acidic urine, pink in alkaline urine
Senna	Yellow-brown in acidic urine, pink to red in alkaline urine, brown on standing
Sulphasalazine	Orange-yellow in alkaline urine
Sulphonamides (antibacterial)	Rust yellow to brown

Table 19. CONTINUED\*

<i>Drug/drug class</i>	<i>Colour produced</i>
Thiazolsulfone	Pink or red
Tolonium	Blue-green
Triamterene	Pale blue fluorescence
Warfarin	Orange

\*Source: Yosselson-Superstine (1996).

the most valuable laboratory tools in clinical practice. Not only does it provide an excellent estimation of the patients kidney function, but it also serves as a guide to dosage adjustments of drugs whose elimination is mainly by the renal route. Colouration of urine can greatly impede the reliability of this measurement.

Two major techniques are used today for the analysis of creatinine: colourimetric and enzymatic. The colourimetric method is based on Jaffé's reaction (Jaffé, 1886) in which saturated picric acid reacts with creatinine in an alkaline medium. This is still in common for the determination of creatinine in serum or urine and is employed in many reagent kits, such as Beckman ASTRA-8, Technicon SMAC and Du Pont ACA. The coloured end product of the reaction absorbs light between 490 and 520 nm and is measured by spectrophotometer. The Jaffé reaction is influenced by non-creatinine chromagens in the samples (Narayanan and Appleton, 1980). These chromagens can be physiological substances such as glucose or protein and also medications like specific cephalosporins (cefoxitin, cephalexin, cafazolin), penicillins, lactulose, high-dose frusemide, methyldopa, acetohexamide, and phenacemide. The many publications on the interferences of these medications, and especially cephalosporins with the Jaffé analysis have been extensively evaluated in a review by Ducharme *et al.* (1993).

Other examples of both classes of interferences have been given by Yosselson-Superstine (1996) in her comprehensive review. In previous times, physicians considered that the visual examination of urine was a considerable diagnostic aid, indeed they were cartooned as 'Piss-pot prophets'. It is fortunate therefore that they did not have to cope with todays plethora of drugs which discolour urine (*Table 19*).

Immunoassays are gaining more use as methods of choice in biochemical and analytical laboratories, for instance in deposition studies for biotechnology products or in therapeutic drug monitoring (TDM) (Bottorff and Stewart, 1986). Various types of immunoassays are employed, the most frequently used being the homogeneous enzyme multiplied immunotechnique (EMIT), enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and fluorescence immunoassay (FIA). All of these assays involve antigen-antibody reactions, so one important mechanism of drug interference with these methods is that involving non-specificity of antibodies (Yosselson-Superstine, 1996). This has been particularly troublesome with the assay of digoxin due to the cross-reactivity of digoxin metabolites and the presence of endogenous digoxin-like immunoreactive substances in the serum. These substances accumulate in the blood, especially in neonates, during the third trimester of pregnancy and in renal failure and liver disease (Morris *et al.*, 1990).

Two metabolites of the diuretic spironolactone, canrenone and its 20-hydroxy

derivative have more cross-reactivity with digoxin than the parent drug (Huffman, 1974; Silber *et al.*, 1979; Morris *et al.*, 1987). Endogenous steroids are also known to cross-react with digoxin (Soldin *et al.*, 1984; Gault *et al.*, 1985) as also Fab fragments infused into patients with digoxin toxicity (Natowicz and Shaw, 1991). Yosseelson-Superstine (1996) has described the procedures that are currently being used to reduce this analytical interference, these procedures follow the guidelines drawn up by the Expert Panel on Drug Effects in Clinical Chemistry of the International Federation of Clinical Chemistry (Galteau and Siest, 1984).

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# PART 2

## Drug Interaction Tables

### Notes on Interpretation of Drug Interaction Tables

The drug interactions cited in these tables refer in the main to clinically relevant drug interactions known to occur in man, and of which there are usually several reported cases in the world literature. Exceptions to this principle have been made where a drug interaction is well known to occur with a closely related chemical compound and where animal data or some clinical evidence indicate that a similar reaction may occur with the mentioned compound. We have not hesitated to cite the *ABPI Data Sheet Compendium* as a reference source, where necessary, since information known to the manufacturer, and frequently not yet published in the medical or pharmaceutical literature, is often cited in individual product data sheets for the first time.

In these tables, we have reported drug interactions under official or INN names; we have avoided the use of proprietary names since these are voluminous, and are frequently different from country to country. Such names are readily available in *MIMS*, *Index Nominum* and similar publications. The order of the tables, broadly follows the classification of the chapters and sections used in the *British National Formulary*. The figures in parentheses refer to abbreviated references at the end of the respective tables.

To avoid loss of information about interactions that arise whilst the book is being printed we have arranged with Elsevier to print Chapter 16 of the Drug Interaction Tables, “Recent and unconfirmed drug interactions”, as late as possible so that we can record clinically important interactions that are published in the medical or pharmaceutical literature whilst our book is being printed and assembled.

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# **CHAPTER 1**

**Drug Interactions with Agents Used to Treat  
Gastrointestinal Disease**

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# **SECTION I. INTERACTIONS WITH AGENTS USED TO TREAT PEPTIC ULCERATION AND OTHER UPPER GASTROINTESTINAL DISORDERS**

## **1.1. PROTON PUMP INHIBITORS**

**OMEPRAZOLE**

**LANSOPRAZOLE**

**PANTOPRAZOLE**

**Therapeutic class and  
Uses**

Both omeprazole and lansoprazole inhibit gastric acid production by blocking the hydrogen-potassium adenosine triphosphate system (the 'proton pump'). They are used in the treatment of gastric and duodenal ulcers and for erosive and reflux oesophagitis. Peptic ulceration and probably stomach cancer are causally related to *Helicobacter pylori* infection of the gastric and duodenal mucosa. Omeprazole is the drug of choice to be used with combined antibiotic therapy in *Helicobacter pylori* eradication programmes.

*Regimens recommended*

Omeprazole + amoxycillin for 14 days

Omeprazole + amoxycillin + metronidazole for 7 days

Omeprazole + clarithromycin

**Side effects**

Omeprazole is used to inhibit excessive acid production in Zollinger Ellison syndrome: skin rash, urticaria and pruritis have been reported, also somnolence, insomnia, vertigo, mental confusion, agitation, depression and hallucinations. Arthritic and myalgic symptoms have been reported but resolve on cessation of therapy (1). Blurred vision and taste disturbance have also been reported. Blood dyscrasias associated with omeprazole are leucopenia and thrombocytopenia. In patients with pre-existing liver disease, hepatitis

with or without jaundice encephalopathy may develop. Increases in liver enzymes in otherwise asymptomatic patients have occasionally been recorded.

At the present time there is inadequate data to draw up a meaningful spectrum of lansoprazole's side effects.

Lansoprazole is a weak inducer of cytochrome P450, however, the drug has been too recently introduced to determine whether or not this could be clinically significant.

#### **Recorded interactions (2-5)**

Omeprazole can delay the elimination of diazepam, phenytoin and warfarin. Monitoring patients receiving warfarin or phenytoin is recommended and a reduction in warfarin or phenytoin dose may be necessary when omeprazole is added to an established treatment regimen with either of these two drugs.

A 54% decrease in the clearance of diazepam and a 130% increase in the half life of diazepam has been reported (3). *In vitro* studies using human liver microsomes showed the conversion of diazepam to nordiazepam was not affected by omeprazole, the conversion of diazepam to 3-hydroxydiazepam was inhibited. The principle metabolite of omeprazole, omeprazole sulphone inhibited both metabolic pathways of diazepam (4).

There is no evidence of interaction with theophylline, propranolol, metoprolol, lidocaine, quinidine, amoxycillin or antacids.

The absorption of omeprazole is not affected by food or alcohol.

Simultaneous treatment with omeprazole and digoxin leads to a 10% increase in the bioavailability of digoxin due to increased gastric pH.

No pharmacokinetic interaction between diazepam and pantoprazole was observed in 12 human volunteers (5).

#### **Extent of clinical use**

Over 100 million treatment courses of omeprazole have been prescribed world wide and it is currently one of the two most widely prescribed medicines. In 1994 prescriptions on FP10 and GP10 cost the British NHS £187 million or 4.78% of all FHSA medicines costs.

Lansoprazole has been too recently introduced to

estimate its impact on the NHS medicines bill. In 1994 it accounted for £6 million or 0.15% of prescription costs on FP10 or GP10 to the British NHS medicines bill.

## **1.2. HISTAMINE<sub>2</sub> RECEPTOR BLOCKING AGENTS**

**CIMETIDINE**

**FAMOTIDINE**

**NIZATIDINE**

**RANITIDINE**

**Therapeutic class and  
Uses**

Cimetidine, famotidine, nizatide and ranitidine are histamine<sub>2</sub> receptor antagonists (H<sub>2</sub>RA). They inhibit basal and stimulated secretion of gastric acid reducing both volume, acid and pepsin content.

H<sub>2</sub>RA are used for the treatment of gastric and duodenal ulcers, oesophageal reflux and Zollinger Ellison syndrome.

They are also used before general anaesthesia in patients at risk of acid aspiration into the lungs (Mendelson's syndrome), particularly in obstetric patients.

H<sub>2</sub>RA are also used in conjunction with NSAIDs to counteract gastro intestinal ulcerogenic activity.

*Helicobacter pylori* eradication

*Helicobacter pylori* is now recognized as the causative organism in most cases of peptic ulceration. It has also been classified as a Class I carcinogen. H<sub>2</sub>RA are used in combination with various antibiotic regimens to eliminate *Helicobacter pylori*.

**Side effects**

Transient and reversible changes in liver function can occur and there have been reports of hepatocellular, hepatocanalicular and mixed hepatitis with and without jaundice. Acute pancreatitis has been reported with several members of this therapeutic class.

Leucopenia and thrombocytopenia have been reported but are rare, as is agranulocytosis and pancytopenia.

Hypersensitivity reactions such as urticaria, angioneurotic oedema, fever bronchospasm, hypotension and anaphylaxis and toxic epidermal necrosis have been reported.

H<sub>2</sub>RA can cause bradycardia, AV block and asystole.

Arthralgia and myalgia have been reported.

Cimetidine has, unlike the other H<sub>2</sub>RA drugs, been shown to cause gynaecomastia and impotence. The relative risks of gynaecomastia for misoprostol, omeprazole, cimetidine and ranitidine were 2.0, 0.6, 7.2 and 1.6 (6).

All H<sub>2</sub>RA have been reported to be secreted in human milk, they should therefore be used with caution in lactating mothers.

**Interactions due to inhibition of cytochrome P450**

Cimetidine retards oxidative hepatic drug metabolism by binding to microsomal cytochrome P450.

Cimetidine by this mechanism prolongs the effective half life of oral anticoagulants, phenytoin, theophylline, intravenous lignocaine, and these interactions are of clinical significance.

Flecainide plasma concentrations are increased by 30% and half life increased by 10% in patients who have concomitantly received cimetidine for more than 1 week with increased risk of cardiac side effects.

Cimetidine also slows the metabolism of diazepam and propranolol.

Famotidine, nizatide and ranitidine do not inhibit hepatic cytochrome P450 and therefore do not potentiate the actions of drugs which are inactivated by this system, e.g. diazepam, phenytoin, lignocaine, propranolol, theophylline and warfarin.

Ranitidine absorption is not affected by food or antacids.

H<sub>2</sub>RA antagonists may increase the absorption of salicylates.

**Extent of clinical use**

Cimetidine, famotidine, nizatide and ranitidine accounted for 1.18, 0.14, 0.19 and 4.76%, respectively, of the cost of all NHS prescriptions written on FP10 or GP10 in the United Kingdom in 1994 or 6.27% or £245 million of the total FHSA medicines bill.

*Combination*

**Anticoagulant/H<sub>2</sub> receptor antagonist**  
e.g. cimetidine (7–19)

*Interaction*

Studies in normal subjects and in patients have shown that cimetidine interacts with stabilized warfarin regimens to increase blood clotting ratio and prothrombin by about 20%; plasma warfarin concentrations almost doubled. Mechanisms have

<i>Combination</i>	<i>Interaction</i>
	<p>been attributed to inhibition of warfarin metabolism (7–13). One controlled study investigating the effects of cimetidine in a large population of patients receiving stable warfarin regimens studied the effect of two dosage regimens of cimetidine (300 mg qds or 800 mg daily at bedtime for 15 days) in a cross-over study on prothrombin time ratios (PTRs) of 27 patients stabilized on conservative warfarin regimens giving a PTR of 1.2–2.0.</p> <p>The PRT increased with both cimetidine regimens, although the mean PRT remained within current recommendations for anticoagulation. The mean PRT after stabilization on cimetidine ranged from 1.65 to 1.75 for the 800-mg dose at bedtime, and from 1.70 to 1.82 for the 300-mg × 4/day regimen. Only two patients achieved prothrombin times (PTs) of 30 sec (upper limit of desired anticoagulation) and the maximum PT was 30.5 sec. Warfarin AUCs increased significantly with either regimen (39% for ×4/day and 21% for bedtime administration). The addition of the two regimens of cimetidine dosage to a stabilized warfarin regimen did not lead to any serious degree of anticoagulation, despite decreased warfarin clearance. Nonetheless, cimetidine did increase PTRs and serum warfarin concentrations, so the prothrombin time should be monitored when cimetidine is added to anticoagulant therapy (14).</p> <p>Cimetidine interacts with the R- but not the S-isomer of warfarin (15–17).</p>
ranitidine (18)	In contrast, ranitidine does not affect the anticoagulant action of warfarin, since it is without an inhibitory effect on hepatic P450 enzyme systems (95).
phenprocoumon/ cimetidine (19)	Cimetidine (400 mg bid) given to 10 patients taking phenprocoumon (9–22.5 mg/week) did not affect anticoagulant control or plasma phenprocoumon levels. Phenprocoumon is excreted predominantly after glucuronidation, thus cimetidine, which acts upon mixed functional oxidase systems in the liver, does not influence this metabolism. It was suggested that cimetidine can be combined with phenprocoumon

<i>Combination</i>	<i>Interaction</i>
phenprocoumon/ imetonidine (19) <i>cont.</i>	without increasing the risk of bleeding complications (19).
<b>Antiepileptic agents/H<sub>2</sub> receptor antagonist</b> e.g. carbamazepine (20) phenytoin (21)	Eleven epileptic patients taking regular carbamazepine or carbamazepine and phenytoin were treated with cimetidine 300 mg tds for 7 or 10 days (17). No change in carbamazepine steady-state plasma levels was observed. A mean rise in phenytoin levels of 27% was found by 1 week. Cimetidine (400 mg daily) caused increased plasma carbamazepine concentrations and neurological toxicity in an elderly woman who had been successfully treated with carbamazepine (600 mg daily) for 20 years for trigeminal neuralgia (21).
<b>Cisapride/H receptor antagonist</b> e.g. cimetidine (22) ranitidine (96)	Enhanced cisapride bioavailability and accelerated cimetidine absorption (22). Cisapride has also been shown to increase the rate of ranitidine absorption (96).
<b>Cyclosporin/H<sub>2</sub> receptor antagonists</b> e.g. cimetidine (23-27)	Cimetidine prolongs the half-life of cyclosporin and increases the serum levels.
<b>Local anaesthetics/H<sub>2</sub> receptor antagonists</b> e.g. cimetidine, ranitidine	Studies of the effect of H <sub>2</sub> -receptor antagonists on the pharmacokinetics of bupivacaine have yielded variable results. While one group of investigators found that pretreatment with ranitidine has either increased plasma concentrations of bupivacaine (31) or had no significant effect (30). Cimetidine (300 mg qid for 1 day) given to six normal subjects reduced the systemic clearance of lignocaine (lidocaine) (1 mg/kg by 10 min i.v. infusion) from 766 to 47 ml/min; the apparent volume of distribution at steady state and the degree of plasma protein binding of lignocaine were also decreased. Five of the six subjects noted lignocaine toxicity during the cimetidine infusion when peak lignocaine concentration was raised by a mean of 50% (32). The mechanism of this interaction appears to be multifactorial, involving both altered distribution and

<i>Combination</i>	<i>Interaction</i>
<b>Procainamide/H<sub>2</sub> receptor antagonist</b> e.g. cimetidine (35–38)	clearance; these are likely to be due to cimetidine's known inhibition of oxidative pathways of biotransformation causing impaired metabolism of lignocaine and an induced decrease in liver blood flow via its vasoconstrictor effects on splanchnic circulation. Side effects should be anticipated when i.v. lignocaine is given to patients also receiving cimetidine. The total dose of lignocaine should be infused slowly or given by repeated small doses. Another report (34) cautions against routine administration of cimetidine to patients receiving lignocaine unless serum lignocaine levels are monitored or the dose of lignocaine is adjusted to counterbalance the enhanced and potentially toxic effects.
<b>Suxamethonium/H<sub>2</sub> receptor antagonists</b> (39–41)	Cimetidine increases the procainamide plasma concentrations by reducing the renal clearance of procainamide
<b>Theophylline/H<sub>2</sub> receptor antagonists</b> e.g. ranitidine famotidine etinidine	There are conflicting reports on the effect of cimetidine on the neuromuscular blocking activity of suxamethonium. Prolonged paralysis (39) and lack of interaction have been reported (40). Famotidine and ranitidine have been reported not to interact with suxamethonium (41).
cimetidine	Comparative studies have suggested that ranitidine does not significantly inhibit theophylline metabolism (46–51) even at very high dosage (50), although there have been occasional reports of theophylline toxicity after concomitant ranitidine therapy (51–53).  Famotidine does not alter theophylline disposition (54) but etinidine reduced the clearance of theophylline and prolonged its elimination half-life (55).  In contrast, cimetidine (1 g/day for 7 days) induced a 35% fall in systemic clearance of theophylline under the same conditions (e.g. 30 min i.v. infusion of theophylline (69). An early report indicated that the elimination half-life of theophylline was increased by a mean of 60% after

cimetidine  
*cont.*

cimetidine administration (56). More detailed studies have shown that cimetidine significantly decreased theophylline clearance by a mean of 39%; the apparent volume of distribution was unchanged, whereas the elimination rate constant was significantly decreased by a mean of 42%. This corresponded to an average increase in elimination half-life of 73% (57). Other studies in young and elderly patients (47–50) and in healthy subjects (63–64) have produced similar findings. The mechanism of this interaction is thought to be the inhibitory effect of cimetidine on hepatic microsomal mixed-function oxidases such as cytochrome P450 and P448 (57, 64, 65). Three cases have been reported in which cimetidine apparently reduced the rate of metabolism of aminophylline. The first of these (66) cimetidine (300 mg qid) in an elderly patient and evoked a grand mal seizure; her EEG was consistent with a toxic or cerebral process. Large doses of aminophylline had been used before cimetidine was started without any complications. In the second case (67) theophylline clearance was 4.75 litres/hr before and 1.17 litres/hr during cimetidine (300 mg qid) treatment, and theophylline half-life increased from 2.7 to 7.8 hr. Steady-state theophylline levels rose from 4.2 µg/ml before cimetidine to 25.7 µg/ml during cimetidine treatment. The third case (67) had end-stage liver disease; her theophylline half-life was tremendously long (118.8 hr) and termination of cimetidine reduced this to 65.2 hr. During cimetidine dosage her serum theophylline concentration was 41.2 µg/ml. She died after liver failure. The rapid decrease in theophylline half-life in this patient and the fact that cimetidine is not extensively metabolized has suggested that cimetidine reversibly binds to the enzyme systems that metabolize theophylline without actually interfering with the intrinsic activity. It has been suggested that the cimetidine–theophylline interaction does not occur in the liver, and that theophylline forms a complex with cimetidine in the blood, thus preventing theophylline from being metabolized (68).

### 1.3. OTHER AGENTS

#### 1.3.1. PROSTAGLANDIN ANALOGUES

##### MISOPROSTOL

**Therapeutic class and  
Uses**

A synthetic prostaglandin analogue used in the treatment of gastric and duodenal ulceration and in the prevention of NSAID-associated ulceration. In a study by Maide and Madhok (70) involving 9000 patients, there was a 50% lower incidence of gastrointestinal symptoms in the misoprostol-treated group compared with an untreated group when given NSAIDs. However, Shield and Morant (71) have pointed out that 132 patients would have to be treated with misoprostol to prevent one ADR associated with taking NSAIDs.

**Side effects**

Hypotension  
Increases uterine tone and should not be used in pregnancy  
Causes abnormal intramenstrual bleedings  
Post-menopausal bleeding  
Menorrhagia  
Diarrhoea  
Abdominal pain, dyspepsia, flatulence, nausea, vomiting  
Rashes  
Dizziness

**Reported interactions**

In extensive studies no clinically significant drug interaction has been attributed to misoprostol.

#### 1.3.2. CHELATES AND COMPLEXES

##### TRIPOTASSIUM DICITRATO BISMUTHATE (De Nol)

**Therapeutic class and  
Uses**

Gastric and duodenal ulcerations  
Used in *Helicobacter pylori* eradication programmes in combination with amoxycillin or amoxycillin and metronidazole. It is thought to have a direct toxic effect on *Helicobacter pylori*.

**Side effects**

Encephalopathy associated with older bismuth subnitrate preparations has not been reported with De Nol.

May darken the tongue and blacken faeces  
Nausea, vomiting.

<i>Combination</i>	<i>Interaction</i>
Tetracyclines/De Nol	Absorption of tetracyclines impaired due to chelation.
Omeprazole/De Nol (72)	Pretreatment with omeprazole resulted in an approximately 300% increase in the absorption of bismuth from tripotassium-dicitrato-bismuthate in six healthy subjects. The mechanism was thought to be the reduction in gastric pH produced by omeprazole.

### 1.3.3. SUCRALFATE

<b>Therapeutic class and Uses</b>	Sucralfate is a combination of Al(OH) <sub>2</sub> and sulphated sucrose. It is used to treat gastric and duodenal ulceration, also chronic gastritis.
<b>Side effects</b>	Constipation, diarrhoea, nausea, indigestion, dry mouth, rash back pain, dizziness, insomnia, vertigo and drowsiness
<b>Interactions</b>	Interactions with sucralfate are all due to impaired absorption.

<i>Combination</i>	<i>Interaction</i>
<b>Antibacterials/sucralfate (74)</b>	Reduced absorption of fluoroquinolone antibacterials and tetracyclines.
<b>Anticoagulants/sucralfate (75)</b>	Absorption of coumarins has been reported to be reduced.
<b>Antiepileptics/sucralfate (71)</b>	Reduced absorption of phenytoin.
<b>Antifungals/sucralfate (71)</b>	Reduced absorption of ketoconazole.
<b>Cardiac glycosides/sucralfate e.g. digoxin (73, 74)</b>	Reduced absorption of digoxin. A case has been reported of a 71-year-old woman who displayed altered absorption of three other medications namely digoxin,

<i>Combination</i>	<i>Interaction</i>
	quinidine sulphate, and warfarin sodium after being given sucralfate. The administration of sucralfate resulted in subtherapeutic serum concentrations of digoxin and quinidine, and also reduced the patient's prothrombin time (PT). Discontinuation of sucralfate increased PT and re-established therapeutic concentrations of digoxin, quinidine, and warfarin. Patients receiving sucralfate concomitantly with digoxin, quinidine, and warfarin should be monitored frequently with regard to serum drug concentration and disease symptomatology.
<b>Thyroxine/sucralfate (74)</b>	Reduced absorption of oral thyroxine.
<b>1.3.4. LIQUORICE DERIVATIVES</b>	
<b>CARBENOXOLONE</b>	
<b>DEGLYCORHIZINISED LIQUORICE</b>	(Caved S contains 380 mg deglycyrrhizinised liquorice contains aluminium hydroxide and bismuth subnitrate)
<b>Therapeutic class and indications</b>	Liquorice derivatives used in the treatment of gastric and duodenal ulceration. The efficacy of these preparations is low compared to H <sub>2</sub> RA and proton pump inhibitors, and they are virtually obsolete as therapy.
<b>Side effects</b>	Carbonoxolone sodium induces salt and water retention, hypokalaemia leading to impaired neuromuscular function and muscle and renal damage with prolonged treatment. Caved S a preparation containing deglycyrrhizinised liquorice contains Al <sup>2+</sup> and bismuth.
<b>Drug interactions</b>	<i>for Caved S see also interactions with Al<sup>2+</sup> and Bismuth salts</i>

<i>Combination</i>	<i>Interaction</i>
<b>Anti-arrhythmics/ liquorice derivatives (76, 77)</b>	The urinary excretion of flecainide, mexiletine and quinidine are reduced.
<b>Antibacterials/liquorice derivatives (76, 77)</b>	The absorption of ciprofloxacin, ofloxacin, pivampicillin, rifampicin, tetracyclines, tетraconazole and ketoconazole are reduced.
<b>Antihypertensives/ liquorice derivatives (76, 77)</b>	Carbenoxolone causes sodium and water retention and therefore antagonizes the effects of anti hypertensive therapy.
<b>Cardiac glycosides/liquorice derivatives (76, 77)</b>	Increased digoxin toxicity if carbenoxolone-induced hypokalaemia occurs.
<b>Corticosteroids/ liquorice derivatives (76,77)</b>	Increased risk of hypokalaemia.
<b>Diuretics/liquorice derivatives (76, 77)</b>	Antagonism of diuretic effect by propensity for carbenoxalone to induce sodium and water retention. Increased risk of hypokalaemia with acetazolamide, thiazide and loop diuretics. Amiloride and spironolactone inhibit carbenoxolone's ulcer healing actions.
<b>Other agents/liquorice derivatives (76, 77)</b>	The absorption of a variety of unrelated compounds may be reduced by carbenoxolone, e.g. chloroquine, hydroxychloroquine, phenothiazines, oral iron, dipyridamole, penicillamine.
<b>Extent of Clinical Use</b>	The 'other drugs' covered in this section used in the treatment of gastric and duodenal ulcer currently only have a very minor role in terms of market volume in the United Kingdom. Misoprostol (Cytotec) had the largest market share in this group and FP10 and GP10 prescriptions in 1994 amounted to £3 million or 0.07% of the FHSAs medicines bill.

### **1.3.5. ALUMINIUM AND MAGNESIUM CONTAINING ANTACIDS**

**ALUMINIUM HYDROXIDE**

**MAGNESIUM CARBONATE**

**MAGNESIUM TRISILICATE**

**ALUMINIUM/MAGNESIUM COMPLEXES**

**Hydroxycarbonate**

**Magaldrate**

**Co-magaldrax**

### **ALUMINIUM AND MAGNESIUM CONTAINING ANTACIDS WITH OTHER INGREDIENTS**

e.g. Dimethicone

e.g. Asilone sodium alginate

e.g. Gaviscon

### **BICARBONATES**

**Therapeutic class and uses** Antacids are preparations designed to neutralize gastric acid.

**Side effects** Magnesium salts tend also to have a laxative action, aluminium salts to cause constipation.

**Reported drug interactions** Interactions are largely due to  $\text{Al}^{2+}$  or  $\text{Mg}^{2+}$  ions chelating with the drug being absorbed, e.g. tetracyclines, or affect absorption or excretion of drugs which are pH dependent.

#### *Combination*

#### *Interaction*

**ACE inhibitors/antacids (78)** Co-administration of antacids with fosinopril or other ACE inhibitors has been shown to reduce serum levels and urinary excretion.

**Aspirin/antacids** Excretion of aspirin is increased in alkaline urine, (forced alkaline diuresis is standard treatment of aspirin overdose). Antacids increase excretion and reduce analgesic effect of aspirin.

**Anti-arrhythmic agents/antacids (78)** Excretion of quinidine is reduced in alkaline urine thus increasing risk of quinidine toxicity.

<i>Combination</i>	<i>Interaction</i>
<b>Antibacterials/antacids (80–87)</b>	Al <sup>2+</sup> and Mg <sup>2+</sup> ions chelate with tetracycline (80), chlortetracycline (81) and form insoluble complexes. The absorption of other antibacterials is inhibited due purely to a pH effect, e.g. azithromycin (84) cefpodoxime (87) ciprofloxacin (83) ethambutol (82) isoniazid (87) nitrofurantoin (72) norfloxacin (87) oxafloxacin (87) pivampicillin (85) rifampicin (86)
<b>Antifungals/antacids (87)</b>	Antacids reduce absorption of imidazole derivatives itraconazole and ketoconazole.
<b>Antiepileptics/antacids (87)</b>	Antacids reduce the absorption of gabapentin and phenytoin.
<b>Biphosphonates/ antacids (88–92)</b>	Antacids reduce absorption of all the bisphosphate group of drugs, e.g. disodium etidronate disodium pamidronate sodium clodronate tiludronate
<b>Cardiac glycosides/ antacids e.g. digoxin (93)</b>	Magnesium trisilicate has been shown to reduce digoxin absorption.
<b>Chlorpromazine/ antacids (94)</b>	Aluminium and magnesium containing antacids reduce the absorption of chlorpromazine.
<b>Iron/antacids (87)</b>	Magnesium trisilicate reduces the absorption of oral iron.

<i>Combination</i>	<i>Interaction</i>
<b>Lithium/antacids (87)</b>	Sodium bicarbonate increases excretion of lithium and therefore reduces plasma lithium concentrations.
<b>Penicillamine/antacids (87)</b>	Antacids reduce penicillamine absorption.

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## **SECTION II. DRUGS AFFECTING GASTROINTESTINAL MOTILITY**

### **1. CISAPRIDE**

Cisapride is described as a gastrointestinal prokinetic agent which stimulates lower oesophageal, gastric, small intestinal and colonic motility. It is used in the treatment of dyspepsia, gastrointestinal reflux and impaired gastric motility. Cisapride has been reported to be associated with prolongation of the QT interval and since it is metabolized by the cytochrome P450 3A4 system, co-administration with any drug that can impair cisapride's hepatic metabolism or itself can cause QT interval is contraindicated since the risk of *torsade de pointes* and ventricular fibrillation is increased.

Cisapride should be used with caution in patients with conditions associated with QT prolongation such as congenital QT syndrome, or patients with electrolyte disturbances.

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulants/ cisapride (97)</b>	Cisapride increases the rate of gastric emptying and intestinal motility is increased. Absorption of warfarin is affected and prothrombin time is increased. Prothrombin time should be checked a few days after initiating or discontinuing cisapride treatment.
<b>Anticonvulsants/ cisapride (97)</b>	Cisapride can affect the absorption of anticonvulsants, and if cisapride treatment is initiated it is advisable to measure the plasma concentrations of antiepileptic drugs several days after initiation or discontinuation of cisapride therapy.

<i>Combination</i>	<i>Interaction</i>
<b>Antibacterial agents/cisapride</b> clarithromycin (95) erythromycin (95)	Macrolide antibiotics, e.g. erythromycin and clarithromycin, inhibit the metabolism of cisapride. This leads to prolongation of QT interval and <i>torsade de pointes</i> or ventricular fibrillation. The Committee on Safety of Medicines (1996) drew attention to eight such cases associated with erythromycin and three cases such associated with clarithromycin.
<b>Antifungal agents/cisapride</b> fluconazole (95) itraconazole (95, 97) ketoconazole (95, 97) miconazole (96, 97)	Antifungal agents of the imidazole type have been shown to inhibit cisapride metabolism by the cytochrome P450 3A4 system and result in prolongation of the QT interval leading to <i>torsade de pointes</i> or ventricular fibrillation.
<b>Drugs prolonging QT interval/cisapride (95)</b>	In March 1996 the Committee on Safety of medicines reported six such cases associated with fluconazole, two cases each with ketoconazole and itraconazole and one case with miconazole.
<b>H<sub>2</sub> Receptor antagonists/cisapride,</b> e.g. cimetidine (22, 96, 97) e.g. ranitidine (96, 97)	<p>As a general rule cisapride should not be used with other drugs that have a propensity to increase the QT interval. e.g.</p> <p><b>Antiarrhythmics</b> quinidine, procainamide, disopyramide, amiodarone sotalol</p> <p><b>Antipsychotics</b> pimozide and thioridazine in particular</p> <p><b>Antihistamines</b> terfenadine and astemizole</p> <p><b>Antimalarials</b> halofantrine.</p> <p>Cisapride bioavailability is increased due to accelerated absorption when given to cimetidine-treated subjects. Increased bioavailability of cisapride may enhance its effects on prolongation of QT interval.</p> <p>Peak plasma concentrations of ranitidine were achieved more rapidly in 12 healthy subjects who took cisapride concomitantly with ranitidine dosage than when they took ranitidine alone.</p>

## 2. METOCLOPRAMIDE HYDROCHLORIDE

Metoclopramide hydrochloride stimulates motility in the upper gastrointestinal tract, and is used in the management of nausea, vomiting, gastro-oesophageal reflux and stasis. It is a dopamine-receptor antagonist and as such can give rise to extrapyramidal symptoms such as parkinsonism and tardive dyskinesia (these reactions are much more common in children and the drug should not be given to children under 14 years of age). Prolactin secretion may be stimulated causing galactorrhoea.

Neuroleptic malignant syndrome has also been reported as a rare complication. This manifests itself with muscular rigidity, fever, raised creatine phosphokinase leucocytosis and loss of consciousness. Blood dyscrasias, aldosteronism, hypotension and effects on mental state, e.g. depression, uncontrolled crying, and delirium have all been reported as side effects of metoclopramide.

<i>Combination</i>	<i>Interaction</i>
carbamazepine/ metoclopramide (98)	Neurotoxicity has been observed in a patient receiving carbamazepine and metoclopramide.

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# **SECTION III. DRUGS USED TO TREAT INFLAMMATORY BOWEL DISEASE**

## **1. CORTICOSTEROIDS (see Chapter 6.2)**

## **2. AMINOSALICYLATES**

Aminosalicylates are used in the induction and maintenance of remission in ulcerative colitis and active Crohn's disease.

### *Preparations available*

mesalazine

olsalazine

sulphasalazine

The most widely used member of this group is sulphasalazine and side effects that have been reported with sulphasalazine can be expected with other members of the group.

### *Side effects of sulphasalazine*

Nausea, vomiting, diarrhoea, headache and rashes are common.

More occasionally haematological abnormalities are manifest including megaloblastic anaemia, Heinz body anaemia, neutropenia, thrombocytopenia, agranulocytosis aplastic anaemia. Regular haematological examination is advised monthly on patients on long-term therapy. Stevens-Johnson syndrome, neurotoxicity, lupus erythematosus, fibrosing alveolitis have been reported. Some contact lenses may be stained yellow/orange.

The Committee on Safety of Medicines have advised that patients receiving treatment with any of the aminosalicylates should be told to report any unexplained bleeding, bruising or purpura, sore throat, or fever that occurs to their doctor immediately. A blood count should be performed and treatment discontinued.

Sulphasalazine is a prodrug, in the large bowel, it is metabolized to 5-aminosalicylate which is the locally therapeutically active moiety and sulphapyridine which is absorbed. This breakdown of the prodrug is largely achieved by the bacterial flora in the large bowel.

The rate of elimination of absorbed sulphapyridine is by acetylation to acetyl sulphapyridine and by *O*-glucuronide formation. There is a genetically determined

dimorphism into fast or slow acetylators which affects metabolism and elimination of sulphapyridine.

<i>Combination</i>	<i>Interaction</i>
<b>Antibacterials/ sulphasalazine</b> e.g. ampicillin (100)	Only a small fraction of orally administered sulphasalazine is absorbed, the remainder reaches the colon intact where it is metabolized by azo-reduction to yield sulphapyridine and therapeutically active 5-amino salicylate. Ampicillin reduces the sulphapyridine plasma concentrations and by inference this would reduce the 5-aminosalicylate at the site of action. Ampicillin action on gut flora is thought to be the mechanism.
e.g. rifampicin, ethambutol (99)	In a study of 11 patients maintained on sulphasalazine for the treatment of Crohn's disease, mean plasma concentrations of sulphapyridine and acetyl-sulphapyridine were reduced when they were receiving rifampicin and ethambutol simultaneously. This was believed to be due either to hepatic microsomal induction by rifampicin or to a reduction in the systemic bioavailability of sulphapyridine by the effects of the antibiotics on the intestinal flora. The latter explanation was favoured.
<b>Cardiac glycosides/ sulphasalazine digoxin</b> (102)	The absorption of digoxin may be reduced.
<b>Folate/sulphasalazine</b> (102)	The absorption of dietary folate may be reduced. This is probably the mechanism of production of the megaloblastic anaemia which may occur during sulphasalazine therapy.

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# **CHAPTER 2**

**Drug Interactions with Agents Used in the Treatment of Cardiovascular Disease**

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## **2.1. INTERACTIONS WITH CARDIAC DRUGS**

### **I. POSITIVE IONOTROPIC DRUGS**

#### **(a) Cardiac glycosides**

Acetyl digoxin

Deslanoside

Digitoxin

Digoxin

Lanatoside C

$\beta$ -Methyl digoxin

Prepared Digitalis

The cardiac glycosides have very similar pharmacological action, but differ considerably in their speed and duration of action.

The principal actions of the cardiac glycosides are an increase in the force of myocardial contraction and a reduction in the conductivity of the heart. They are most useful in the treatment of *supraventricular tachycardias*, especially in controlling the ventricular response to atrial fibrillation. *Heart failure* may be improved in patients in sinus rhythm, because of changes in the availability of intracellular calcium.

Cardiac glycosides have little effect on the heart until they are present in the tissues in a concentration near to that at which toxic effects may occur.

Headache, anorexia and nausea may occur with therapeutic doses of cardiac glycosides; but vomiting bradycardia or extrasystoles are evidence of overdosing. Blurring of vision may occur and there may be disturbance of colour vision, objects appearing yellow or green. Potassium depletion due to concurrently used diuretics may precipitate toxicity. Therefore diuretics used in combination with digoxin or other cardiac glycoside should be potassium sparing or should be given with potassium supplements.

Digitalis is slowly cumulative due to its content of digitoxin; prolonged treatment with digitalis may produce gynaecomastia in men, and swelling and breast tenderness in women.

Digitoxin is the most potent of the digitalis glycosides and is also the most cumulative; the toxic effects are similar to those of digitalis, but it is more likely to give rise to extra systoles and ventricular fibrillation. The toxic effects of digoxin

are similar to those of digitalis but it is more rapidly excreted than other digitalis glycosides and therefore less likely to give rise to cumulative effects.

Digoxin and digitoxin are the cardiac glycosides used most widely and they have generally displaced the use of digitalis. Renal function is the most important determinant of digoxin dosage since it is eliminated unchanged by the kidney. Elimination of digitoxin depends on metabolism by the liver.

In patients in mild heart failure a loading dose of digoxin is not required and a steady-state plasma concentration is achieved after about 7 days when digoxin is given in doses of 125 or 250 µg twice per day. When rapid digitalization is required, digoxin (0.75–1.0 mg) may be given intravenously as an infusion over about 2 hr, and this should be followed by the maintenance doses above.

Digitoxin which has a longer half-life need only be given once per day.

Medigoxin ( $\beta$ -methyl digoxin) acts rapidly when given by mouth or intravenously and is similar to digoxin. Lanatoside C is intermediate between digoxin and digitoxin. Digoxin is a urinary metabolite of Lanatoside C.

When digoxin toxicity is such that it cannot be controlled by cessation of digoxin treatment and correction of electrolyte balance, then digoxin-specific antibodies can be used to treat digoxin or digitoxin overdose. Digoxin-specific antibodies (Digibind-Glaxo-Wellcome) are available as a powder for preparation of an intravenous infusion containing 40 mg digoxin-specific antibody fragments (F(ab)).

## b. Phosphodiesterase inhibitors

**Enoximone**

**Milrinone**

Enoximone and milrinone are selective phosphodiesterase inhibitors which exert most of their effect on the myocardium. They administered intravenously in the short-term treatment of congestive heart failure.

Enoximone has positive ionotropic and vasodilator effects which have been sustained over 48 hr. Such short-term treatment has not been observed to be associated with any drug interactions. Enoximone has been used with the diuretics amiloride, triamterine, frusemide, spironolactone, digitalis glycosides,  $\beta$ -adrenergic blockers, lignocaine, nifedipine, procainamide, quinidine, heparin and warfarin without observed interaction (1).

Milrinone is a selective inhibitor of peak III phosphodiesterase isoenzyme in cardiac and vascular muscle. It enhances AV node conduction. Milrinone has been used in fully digitalized patients and produced a further ionotropic effect. Theoretical interaction between milrinone and calcium channel blockers has not been observed clinically. No interactions have been described according to the products data sheet (2).

Physical incompatibility (precipitation) exists if frusemide or bumetanide is mixed with milrinone solution. Sodium bicarbonate intravenous infusion should not be used for dilution of milrinone (2).

## II. ANTI-ARRHYTHMIC AGENTS

Anti-arrhythmic agents can be classified according to their effects on the electrical behaviour of myocardial cells e.g.:

Class I (a) (b) (c):	Membrane stabilising drugs, e.g. Class I (a) quinidine, Class (b) lignocaine, Class (c) flecainide
Class II:	$\beta$ -Adrenergic blockers
Class III:	Amiodarone, bretylium and sotalol (also Class II)
Class IV:	Calcium channel blockers

However, clinically anti-arrhythmic agents can be more meaningfully classified into those that act on supraventricular arrhythmias, or supraventricular and ventricular arrhythmias, and those that act only on ventricular arrhythmias.

1. Supraventricular arrhythmias — adenosine, verapamil
2. Supraventricular and ventricular arrhythmias — amiodarone,  $\beta$ -adrenergic blockers, disopyramide, flecainide, procainamide, quinidine
3. Ventricular arrhythmias — bretylium, lignocaine, mexiletine, phenytoin, propafenone, tocainide

### 1. Supraventricular arrhythmias

#### *Paroxysmal Supraventricular Tachycardia*

**Adenosine** acts by slowing conduction through the AV node. This action can interrupt re-entry circuits involving the AV node and restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias. Once the circuit has been broken the tachycardia stops. Adenosine can be used in the treatment of Wolff-Parkinson-White syndrome. By transiently slowing AV conduction adenosine can induce bradycardia. This can be exploited in the interpretation of ECG recordings and can aid the evaluation of broad or narrow complex tachycardias. Severe bradycardia has been reported and some patients have required temporary pacing. The effects of adenosine are not reversed by atropine.

Adenosine has a short duration of action 8–10 sec, the duration of action is extended by dipyridamole which is a potent inhibitor of adenosine uptake. Asystole has been reported following their concomitant administration.

**Verapamil** is usually effective in the treatment of supraventricular tachycardias. An initial intravenous dose followed by oral treatment is the usual regimen. Hypotension may occur at high doses.

Verapamil should not be used for tachyarrhythmias where the QRS complex is broad. Verapamil should not be used in the treatment of Wolff-Parkinson-White syndrome.

Verapamil should not be injected into patients recently treated with  $\beta$ -adrenergic

blockers, because of the risk of hypotension AV block or even asystole. It may also be dangerous to give verapamil and  $\beta$ -adrenergic blockers together by mouth (3).

### *Atrial Fibrillation*

The ventricular rate can usually be controlled with digoxin. A  $\beta$ -adrenergic blocker may be added if necessary.

The patient should be anticoagulated prior to treatment of atrial fibrillation if the patient has valvular disease or is elderly to minimize the risk of emboli.

### *Atrial Flutter*

**Digoxin** can be used to control ventricular rate. Reversion to sinus rhythm is best achieved by DC shock.

If flutter is of long standing the patient should be anticoagulated before attempting to convert to sinus rhythm, to minimize the risk of emboli.

## **2. Supraventricular and ventricular arrhythmias**

**Amiodarone** is used in the treatment of tachycardia associated with Wolff-Parkinson-White syndrome. It may be used in the treatment of other arrhythmias, but treatment should only be initiated under hospital supervision. Amiodarone may be used under carefully controlled conditions and close supervision for the control of paroxysmal supraventricular tachycardia, nodal and ventricular tachycardia, atrial fibrillation and flutter and ventricular fibrillation.

Patients taking amiodarone develop corneal micro deposits these are usually discernable only by slit-lamp examination and, rarely, give rise to symptoms such as visual haloes. However, drivers can be dazzled by oncoming headlights at night by the severe manifestation of haloes(4). These deposits regress with termination of therapy.

In rare cases optic neuritis may develop. Amiodarone can cause photosensitivity and use of sunblocking creams is recommended.

Amiodarone contains iodine which can be released from the molecule and can cause thyroid dysfunction. Both hypothyroidism and hyperthyroidism have been reported.

Diffuse pulmonary alveolitis and fibrosis have been reported usually presenting as dyspnoea. Alveolitis is claimed to resolve spontaneously on withdrawal of treatment but corticosteroids do assist the resolution of this condition.

Peripheral neuropathy and myopathy may complicate amiodarone therapy.

Amiodarone prolongs the QT interval and should not be used in combination with other drugs that prolong the QT interval (*vide infra*).

**Disopyramide** is able to prevent and control a wide variety of cardiac arrhythmias, probably by slowing conduction in the His-Purkinje system; and by increasing the refractory period in myocardial muscle of both the atrium and ventricles.

Disopyramide should not be used in second- or third-degree heart block. Reduced dosage is recommended in patients with impaired renal function. Disopyramide increases QT interval and should not be used in combination with other drugs which prolong QT interval (5).

Disopyramide has marked antimuscarinic actions and may precipitate dry mouth, blurred vision, urinary retention and should not be given to patients with glaucoma (5) or in patients with prostatic hypertrophy. Disopyramide may precipitate hypoglycaemia.

**Flecainide** is a potent sodium channel blocker, and slows conduction of electrical impulses through cardiac muscle and the conducting system, prolonging the PR interval and widening the QRS complex. Flecainide can be used for Wolff-Parkinson-White syndrome, paroxysmal atrial fibrillation, sustained ventricular tachycardia and premature ventricular beats.

Side effects include dizziness, visual disturbances, arrhythmogenic effects, nausea, photosensitivity, hepatic enzyme changes and jaundice, peripheral neuropathy, pulmonary fibrosis and pneumonitis (6).

**Procainamide** treatment of ventricular arrhythmias, post-infarction induced arrhythmias, atrial fibrillation and Wolff-Parkinson-White syndrome should be initiated in hospital.

Procainamide is metabolized to *N*-acetyl procainamide which increases QT interval and should not be used in combination with other drugs increasing the QT interval (*vide infra*). Procainamide should not be used in patients with second- or third-degree AV block unless a pacemaker is *in situ*. Procainamide should not be used in patients with myasthenia gravis or SLE or bronchial asthma. Procainamide can induce a lupus erythematosus-like syndrome in its own right, as well as serious blood dyscrasias, and angioneurotic oedema (7).

**Quinidine** is used in the suppression of supraventricular and ventricular tachyarrhythmias and in the maintenance of sinus rhythm following cardioversion of atrial fibrillation. Quinidine should be used with caution in patients with impaired AV conduction. Quinidine prolongs the QT interval and should not be used in combination with other drugs that prolong QT interval (8).

### 3. Ventricular arrhythmias

**Bretylium tosylate** is used primarily for the treatment of ventricular fibrillation, and has often proved effective where DC cardioversion has failed. This effect is attributed to its local anaesthetic properties.

It is administered intravenously or intramuscularly but can cause severe hypotension. This effect is due to its ability to interfere with postganglionic sympathetic nervous transmission. Bretylium increases the QT interval and should not be used in combination with other drugs with this potential (*vide infra*) (9, 10).

**Lignocaine hydrochloride** is used in the prevention of ventricular tachyarrhythmias in patients following acute myocardial infarction. AV block is an absolute contraindication (13).

**Mexiletine hydrochloride** is an anti-arrhythmic agent which depresses the maximum rate of depolarization with little or no modification of resting potential or duration of action potential. Mexiletine is used in the treatment of ventricular arrhythmias but should not be used in the first 3 months following myocardial infarction.

Mexiletine can exacerbate certain arrhythmias and cause *torsade de pointes*. Adverse effects include rash, jaundice, arthralgia, fever, thrombocytopenia, Stevens-Johnson syndrome, and pulmonary fibrosis.

**Phenytoin** the use of phenytoin for its membrane stabilizing effects by slow intravenous injection for the treatment, particularly of digitalis-induced ventricular arrhythmias, is now obsolete.

**Propafenone hydrochloride** is a class I anti-arrhythmic agent with basic local anaesthetic and membrane-stabilizing properties. Some  $\beta$ -adrenergic blocking action has also been described. Propafenone decreases the depolarization velocity and slows conduction in the His-Purkinje system with resultant increase in the PR interval and the QRS complex. Propafenone is used in the treatment of paroxysmal supraventricular tachycardias and ventricular arrhythmias.

Propafenone should not be used in uncontrolled cardiac failure, severe obstructive pulmonary disease or marked hypotension. Propafenone may worsen myasthenia gravis (11).

**Tocainide** is used for its membrane-stabilizing properties for the treatment of ventricular tachyarrhythmias. It is contraindicated in patients with second- or third-degree heart block. Rare but reported adverse reactions include bone marrow depression, pulmonary fibrosis, interstitial pneumonitis, Stevens-Johnson syndrome, exfoliative dermatitis and lupus erythematosus-like syndrome (12).

#### 4. Prolongation of QT interval

The QT interval is the duration between the beginning of the QRS complex and the end of the T-wave on the electrocardiogram. Jervell *et al.* (14) described an association between prolonged QT intervals and sudden death. Recent interest has centred on drug-induced prolongation of the QT interval and a functional link to serious ventricular arrhythmias (15) and cardiovascular mortality (16, 17). The prototype arrhythmia is *torsade de pointes* (18). The mechanism underlying the prolongation of the QT interval has been suggested to be an abnormal channel protein reducing on outward repolarizing potassium current or increasing on inward depolarizing calcium or sodium current (20). Prolonged QT intervals, in the presence of a slow heart rate, gives rise to early after depolarizations which can

initiate *torsade de pointes* (triggered arrhythmogenesis). At any given degree of prolongation of QT interval the risk appears to depend more on QT interval dispersion (heterogeneous myocardial changes in repolarization) rather than QT interval *per se* (homogeneous global myocardial changes).

Thomas *et al.* (1996) reviewed the drugs known to produce prolongation of the QT interval. (see Table). It is known that *the co-administration of any two drugs both of which are known to increase the QT interval greatly increases the risk of torsade de pointes and sudden death.*

*Table. DRUGS KNOWN TO PROLONG QT INTERVAL\**

Therapeutic class	Individual drug
Antiarrhythmic agents — Class Ia	disopyramide (5), flecainide, quinidine (22), procainamide (7),
Antiarrhythmic agents — Class III	<i>N</i> -acetyl procainamide, amiodarone (4), nifekalol, sotalol (38), bretylium (9)
Vasodilators	prenylamine (25), cepridil (32)
Psychotropics	Phenothiazines (39), tri- and tetracyclic antidepressants, pimozide (35, 36), haloperidol (37)
Corticosteroids	prednisolone
Diuretics	frusemide
Lipid lowering agents	probucol (21)
Sympathomimetic amines	salbutamol (26), terbutaline (26), fenoterol (26)
Serotonin antagonists	ketanserin (27)
Gastric motility agents	cisapride (28, 33)
Antihistamines	terfenadine (29, 34), astemizole (30)
Anti-microbials	erythromycin and other macrolide antibiotics, chloroquine, halofantrine (24, 31), mefloquine (23), quinine (23)
Drugs used in the treatment of urinary incontinence	terodilane

\*Modified after Thomas *et al.* (20).

## I. INTERACTIONS WITH CARDIAC GLYCOSIDES

<i>Combination</i>	<i>Interaction</i>
ACE inhibitors/digoxin (39)	Captopril increases the plasma concentration of digoxin

<i>Combination</i>	<i>Interaction</i>
<b>Anaesthetics (cyclopropane)/ cardiac glycosides (44)</b>	Cyclopropane anaesthesia may induce signs of digitalis intoxication in patients who are fully digitalized before anaesthesia.
<b>Anion exchange resins/cardiac glycosides (41–43)</b>	Absorption of all cardiac glycosides is reduced by the anion-exchange resins cholestyramine or colestipol. These ion-exchange resins (lipid-regulating agents) interfere with the absorption of digoxin (41, 42). Cholestyramine reduced digitoxin half-life in normal subjects from 141.6 to 84.4 hr. Cholestyramine has been used in the treatment of digitoxin poisoning because it binds with digitoxin excreted in bile and prevents enterohepatic recirculation (43). Alternative cholesterol-lowering agents should be used if they are required in patients being treated with digoxin or digitoxin.
<b>Antacids/cardiac glycosides e.g. activated dimethicone aluminium hydroxide bismuth carbonate calcium carbonate magnesium oxide magnesium peroxide magnesium trisilicate and formulations containing mixtures of these agents (45–49)</b>	The absorption kinetics of digoxin have been shown to be affected in <i>in vitro</i> (45) and <i>in vivo</i> studies (46, 47). Studies using an <i>in vitro</i> model of drug interactions in the rat gut (48) have shown that the absorption of digoxin is reduced by 99.5% in the presence of magnesium trisilicate, 15.3% with light magnesium carbonate, 15.2% with bismuth carbonate, 11.4% with aluminium hydroxide gel, and 3.4% in the presence of a 35% aqueous emulsion of activated dimethicone (49).
	Plasma levels of digoxin are effective only within a narrow therapeutic range, and any factor which will affect its bioavailability will give rise to problems in patients stabilized on this drug. Patients should be warned of this danger.
<b>Anti-arrhythmics/ digoxin (39)</b>	Digoxin plasma levels are increased by amiodarone, flecainide, propafenone, quinidine.
<b>amiodarone/digoxin (50, 51)</b>	Seven patients on steady maintenance digoxin treatment had their plasma digoxin concentrations

<i>Combination</i>	<i>Interaction</i>
	<p>raised by a mean of 69% after taking amiodarone (600 mg daily); four of these patients developed symptoms of digoxin toxicity. Amiodarone may displace tissue-bound digoxin or interfere with digoxin excretion.</p> <p>Sharper increases in digoxin levels (66–800%) have been observed in children. This exaggerated effect was attributed to impaired renal clearance of digoxin due to inhibition of its tubular secretion (this route of clearance being specially important in children) (51).</p>
Quinidine/digoxin	<p>Quinidine causes an increase in serum digoxin concentration in 90% of cases; increase is variable but averages two-fold and the raised levels are maintained (52). It has been suggested that the underlying mechanisms include a quinidine-induced reduction of both renal and non-renal clearance of digoxin. A quinidine induced redistribution of digoxin by displacement from tissue binding sites (57, 58), leading to a reduction in distribution volume (54, 59) followed by decreased renal clearance of digoxin (52–54, 58, 60) which is saturable (68), and this is the determinant of the serum level during the steady state (59). This is suggestive of a reduced binding of digoxin in muscle (61–64). Serum protein binding sites are unlikely to be involved (65). More recent work (66) has shown that raised serum digoxin levels resulting from a digoxin–quinidine interaction in patients with normal renal function is due to a reduction in renal digoxin clearance. Studies have now investigated the extent of the interaction in patients with renal impairment to determine whether an extrarenal mechanism is also involved. Anuric patients also showed a marked but variable increase in serum digoxin levels after quinidine (mean pretreatment, 0.84 ng/ml; post-quinidine, 1.58 ng/ml). Two other experiments showed that quinidine did not affect serum protein binding of digoxin <i>in vitro</i> or <i>in vivo</i>, so reduced renal digoxin clearance is not due to increased serum protein binding. While extrarenal digoxin excretion is of minor importance in normal situations, in anuric patients it becomes the main mechanism of elimination and,</p>

<i>Combination</i>	<i>Interaction</i>
<b>Quinidine/digoxin cont.</b>	<p>because serum digoxin levels increase in such a variable way after quinidine, digoxin dosage should be carefully controlled during combination therapy in such patients.</p> <p>It has been suggested that the digoxin dose be halved (54) before starting quinidine but, due to the variable nature of the interaction, adjustment of digoxin dose should be made 4–5 days after starting quinidine if serum digoxin concentration indicates reduction in dosage is required. Patients should be monitored for signs of too much or too little digoxin (69). The interaction has been shown to have clinical significance (67).</p> <p><i>NB. Serum concentration and effect of digoxin will fall when quinidine is withdrawn from a patient previously stabilized on both drugs (57, 68).</i></p>
<b>Quinidine/digitoxin (69–74)</b>	<p>Although it is well established that a digoxin–quinidine interaction increases plasma digoxin levels (69–70), a corresponding interaction between digitoxin and quinidine is still somewhat controversial. A random cross-over study in 10 normal subjects showed that the two drugs could be taken together without evoking change in digitoxin kinetics (36). These negative findings have been questioned and other studies have shown that digitoxin serum levels increased after starting quinidine (71–74).</p>
<b>Antibacterials/digoxin Erythromycin and other macrolides/digoxin (75– 77, 150)</b>	<p>Erythromycin enhances the effects of digoxin by increasing the plasma level. In approximately 10% of patients given digoxin, substantial conversion of the drug to cardioactive reduced metabolites (digoxin reduction products, DRP) occurs. A 5-day course of erythromycin or tetracycline to three such ‘excretors’ of DRPs markedly reduced or eliminated DRP excretion in urine and stools and serum digoxin concentrations rose as much as two-fold (75–76). Changes in gut flora may enhance digoxin absorption; one case is reported (77) in which an elderly patient showed increased serum digoxin concentration (rise from 1.4 to 2.6 ng/ml) and exhibited signs of toxicity</p>

<i>Combination</i>	<i>Interaction</i>
	(nausea and vomiting) after taking only four doses of erythromycin (250 mg each, oral). An ECG showed an AV junctional rhythm. She was also routinely receiving warfarin and showed a prothrombin time of 47 sec (compared with 25–32 sec previously). Digoxin was stopped and the nausea abated with a return to sinus rhythm. Previous doses of digoxin and warfarin were resumed 1 month later without toxic symptoms. It has previously been shown that gut flora may inactivate digoxin prior to absorption and that antibiotics (e.g. tetracyclines or erythromycin) may counteract this through their action on gut flora. This case history suggests that a small dose of orally administered erythromycin (1g) can alter gut flora substantially, resulting in a concomitantly increased prothrombin time (due to reduced vitamin K production) and an increase in serum digoxin concentrations up to toxic levels (due to reduced digoxin inactivation.) This confirms earlier clinical findings (75) that inactivation of digoxin by gut flora may be reversed by antibiotics resulting in elevation of serum digoxin levels.
	Clarithromycin also increases digoxin levels and this might result in digoxin toxicity. (150)
<b>Neomycin/digoxin (39)</b>	Plasma levels of digoxin are reduced by neomycin.
<b>Rifampicin/digitoxin (79, 80) /digoxin (78)</b>	Rifampicin accelerates the hepatic metabolism of digitoxin (39). Rifampicin reduces the plasma levels of digoxin. A possible interaction between digoxin and rifampicin occurred in a long-term dialysis patient who received i.v. digoxin at the end of each dialysis session. Her serum digoxin levels remained within the accepted therapeutic range. One week after starting antitubercular treatment with rifampicin, her serum digoxin levels fell and she showed signs of heart failure. Substitution of ethambutol for rifampicin without digoxin change permitted serum digoxin levels to rise. It is likely that rifampicin induced the metabolism of a clinically significant fraction of the digoxin administered. This interaction has not been

<i>Combination</i>	<i>Interaction</i>
<b>Rifampicin/digitoxin cont.</b>	reported previously although an interaction between digitoxin and rifampicin had been noted (79, 80).
<b>Tetracycline/digoxin (39)</b>	Tetracycline increases the plasma levels of digoxin.
<b>Trimethoprim/digoxin (81)</b>	Taking trimethoprim (200 mg twice daily for 2 weeks) increased the plasma digoxin level by a mean of 22% in nine patients (mean age 78, all having normal creatinine values) maintained on constant doses of 0.125–0.25 mg digoxin orally; levels exceeded normal (rising from 1.3 to 2.8 nmol/l) in one subject. In contrast, dosing for 10 days with trimethoprim 200 mg twice daily did not affect the total clearance of a single-dose digoxin (1 mg i.v.) in six healthy subjects (mean age 29). In these renal clearance was decreased by 17%, glomerular filtration rate remaining constant. It appears that trimethoprim decreases digoxin clearance in the elderly but not in younger patients, probably by reduced renal tubular secretion. In addition, an alteration in gut flora by trimethoprim may account for an effect on oral digoxin availability not seen after intravenous dosing.
<b>Anticonvulsants/ digoxin and digitoxin (39, 82)</b>	Enzyme-inducing anticonvulsants carbamazepine, phenobarbitone and phenytoin accelerate the hepatic metabolism of digitoxin but do not interact with digoxin.
<b>Antifungals/digoxin Amphotericin B/digoxin (83, 84)</b>	Hypokalaemia may occur during amphotericin therapy and facilitate the development of digitalis toxicity. Treat the potassium deficiency as required.
<b>Itraconazole/digoxin (32)</b>	Plasma level of digoxin is increased by itraconazole
<b>Antimalarial agents/digoxin (82)</b>	Quinine, chloroquine, hydroxy-chloroquine and mefloquine raise the plasma levels of digoxin with increased risk of digitalis toxicity.

<i>Combination</i>	<i>Interaction</i>
	Chloroquine and mefloquine also increase the QT interval.
<b><math>\beta</math>-Adrenergic blockers/cardiac glycosides (82)</b>	When used together there is increased risk of AV block and bradycardia. $\beta$ -Adrenergic blockers and digoxin are used to reduce the ventricular rate in atrial fibrillation and flutter which are not controlled by digoxin alone but the procedure carries a significant risk of inducing AV block.
<b>Calcium channel blockers/digoxin (82)</b>	Plasma concentration of digoxin are increased by diltiazem, nicardipine, nifedipine and verapamil.
Diltiazem/digoxin	A study on the effect of diltiazem on steady-state digoxin levels was performed in 10 healthy subjects. A constant dose of digoxin was given for 45 days. Diltiazem (60 mg 8-hourly) was given on days 18–34. The mean digoxin level rose by 20% after diltiazem was added but did not alter after diltiazem was withdrawn. Patients receiving these two drugs concomitantly should be monitored carefully for 2 weeks after the addition or withdrawal of diltiazem. Similar (but greater) changes have been previously reported with nifedepine and verapamil.
Nifedipine/digoxin (88)	During co-administration of nifedipine (10 mg) and digoxin (0.125 mg tid) to normal subjects, plasma digoxin concentrations rose by a mean of 45% compared with previous levels on digoxin alone. The mechanism of this interaction has not been established.
Verapamil/digoxin (86–88)	In normal subjects verapamil significantly decreased the mean volume of distribution of digoxin from 0.83 to 0.64 l/kg, and digoxin total body clearance from 3.28 to 2.15 ml/min/kg; both renal and extrarenal clearance were impaired. Verapamil may inhibit renal clearance of digoxin by inhibiting tubular secretion. Mean elimination half-life of digoxin increased by 31% (86). Significant increases in digoxin serum concentrations (0.76 to 1.31 ng/ml) have also been reported following the addition of verapamil (240 mg daily) to 49 patients who were previously stabilized on

<i>Combination</i>	<i>Interaction</i>
<b>Verapamil/digoxin cont.</b>	<p>digoxin; symptoms of toxicity occurred in several patients (87).</p> <p>Frequent plasma digoxin measurements and adequate digoxin dosage reduction are recommended to avoid unnecessary risks during the combined use of digoxin and verapamil (86–88).</p>
<b>Calcium salts/cardiac glycosides (82, 89)</b>	<p>Large intravenous doses of calcium salts can precipitate arrhythmias in digitalized patients.</p> <p>A high concentration of calcium is inhibitory to positive inotropic action of digitalis and potentiates toxic effects. <math>\text{Ca}^{2+}</math> causes a dangerous increase in ATP-ase inhibition.</p> <p>Injections of calcium salts should not be given during digitalis therapy, and digitalis (and other cardiac glycosides) should be given cautiously to patients receiving parathyroid extract or large doses of vitamin D (89).</p>
<b>Diuretics/cardiac glycosides (82, 92)</b>	<p>There is an increased risk of toxicity from cardiac glycosides during diuretic treatment with agents that induce hypokalaemia. This may occur with acetazolamide, bumetanide, chlorthalidone, the loop diuretics including ethacrynic acid, frusemide, mefruside, thiazides.</p>
<b>Spironolactone/ digitoxin (43)</b>	<p>Spironolactone increased digitoxin half-life in normal subjects from 141.6 to 192.2 hr.</p> <p>This interaction may be harmful to digitoxin-treated patients if they are given spironolactone as a diuretic with <math>\text{K}^+</math>-sparing effect.</p>
<b>Glucose infusion/cardiac glycosides (93, 94)</b>	<p>A large intake of carbohydrate may worsen or precipitate digitalis toxicity by causing a shift of potassium into the cells with a decrease in serum potassium.</p>
<b>Skeletal muscle relaxants (suxamethonium)/ cardiac glycosides (90, 91)</b>	<p>Suxamethonium appears to potentiate digitalis glycosides with respect to their effect on conduction and ventricular irritability. Arrhythmias have been reported.</p> <p>Anaesthetists should be aware of the possibility of this</p>

<i>Combination</i>	<i>Interaction</i>
<b>Sympathomimetic amines/cardiac glycosides (95, 96)</b>	<p>interaction; neuromuscular blocking drugs other than suxamethonium should be used in digitalized patients.</p> <p>Combination of these drugs results in increased liability to ectopic pacemaker activity. Ephedrine enhances the possibility of arrhythmias in particular. Patients on digitalis glycosides should only be given sympathomimetic drugs with caution.</p> <p>Self medication with OTC medicines containing sympathomimetic amines should be avoided.</p> <p>Pharmacists should enquire whether or not a patient is taking a cardiac glycoside before selling such an OTC product.</p>
<b>Ulcer healing drugs/cardiac glycosides (82, 145)</b>	<p>Carbonoxolone can cause hypokalaemia with increased risk of arrhythmias in digitalized patients. Sucralfate reduces absorption of digoxin and other cardiac glycosides (145)</p>
<b>Miscellaneous gastrointestinally acting drugs/cardiac glycosides (39)</b>	<p>A number of drugs that are used in the treatment of bowel disease, which affect motility by a variety of mechanisms, impair cardiac glycoside absorption, e.g. kaolin-pectin, bulk-laxatives, metoclopramide, diphenoxylate, sulphosalazine. Conversely there is increased absorption of cardiac glycosides with propantheline.</p>

## II. INTERACTIONS WITH ANTI-ARRHYTHMIC AGENTS

Interactions with  $\beta$ -adrenergic blockers and calcium antagonists are dealt with in the chapter on antihypertensive drugs.

## III. INTERACTIONS WITH ADENOSINE

<i>Combination</i>	<i>Interaction</i>
<b>Antiplatelet drugs/adenosine (82)</b>	Dipyridamol increases the plasma level of adenosine. Asystole has been reported following concomitant administration.

*Combination**Interaction*

**Theophylline/  
adenosine (82)** The anti-arrhythmic effect of adenosine is blocked by theophylline.

#### IV. INTERACTIONS WITH AMIODARONE

**Antiarrhythmics/  
amiodarone (5, 7, 27,  
82, 98)** Disopyramide, flecainide, procainamide and quinidine all increase QT interval and this effect increases the risk of *torsade de pointes* since amiodarone also increases QT interval. Amiodarone also increases the plasma concentrations of flecainide, procainamide and quinidine. Two patients treated with a combination of amiodarone and quinidine for minor arrhythmia both developed dangerous atypical ventricular tachycardia (*torsade de pointes*). Both patients had QT interval prolongation. A combination of amiodarone and quinidine given to normal subjects raised the plasma quinidine concentration and prolonged the QT interval, confirming the observation of a clinically important and potentially dangerous interaction between the two drugs. Careful monitoring of the ECG for QT interval prolongation and serum levels of quinidine is indicated when amiodarone is added to quinidine treatment for management of arrhythmias.

**Anticoagulants/  
amiodarone (82, 99,  
100, 101)** The metabolism of nicoumalone and warfarin is inhibited, i.e. the anticoagulant effect is increased with consequent risk of bleeding. Five of nine patients given amiodarone while on established warfarin treatment presented with bleeding phenomena 3–4 weeks later; warfarin dosage required reduction by 30% to re-establish anticoagulant control; these warfarin-potentiating effects persisted up to 4 months after amiodarone was stopped (99). The addition of amiodarone on two occasions led to dangerous increases in the anticoagulant effects of warfarin in one patient (100). Other studies, both animal (100) and human (101) have confirmed this interaction.

<i>Combination</i>	<i>Interaction</i>
<b>Anticonvulsant agents/amiodarone</b> (4, 82)	The metabolism of phenytoin is inhibited leading to increased plasma concentrations and increased risk of phenytoin toxicity. The increased levels of free phenytoin may also be due to plasma protein displacement.
<b>Antihistamines/ amiodarone</b> (4, 29, 30, 34, 82)	Amiodarone increases the QT interval as do astemizole and terfenadine. There is a risk of developing <i>torsade de pointes</i> .
<b>Antimalarials/ amiodarone</b> (4, 23, 24, 31, 82)	Chloroquine, halofantrine, mefloquine and quinine all increase the QT interval as does amiodarone. The risk of <i>torsade de pointes</i> is high.
<b>Anti-psychotic drugs/amiodarone</b> (4, 35, 36, 37, 39)	Phenothiazines and tri- and tetracyclic drugs increase the QT interval and in combination with amiodarone increase the risk of <i>torsade de pointes</i> .
<b>Aprindine/ amiodarone</b> (98–103)	Two cases have been reported in which amiodarone caused increased serum aprindine concentrations concomitant with the appearance of side effects in patients who had achieved steady-state aprindine levels before initiation of amiodarone therapy. Reduction of daily aprindine dosage still yielded aprindine levels higher than those prior to amiodarone. The mechanism has not yet been established but it should be noted that amiodarone has also been reported to increase plasma concentration of warfarin and digoxin (99–102) and quinidine (98) possibly by an effect on their metabolism and on their protein binding. A similar mechanism(s) may apply with aprindine.
<b><math>\beta</math>-Adrenergic blockers/amiodarone</b> (4, 38, 82)	Given in combination with amiodarone, $\beta$ -adrenergic blockers increase the risk of bradycardia and AV block and myocardial depression. Sotalol also increases the QT interval and amiodarone also increases the QT interval and in combination can cause <i>torsade de pointes</i> .

<i>Combination</i>	<i>Interaction</i>
<b>Calcium channel blockers/amiodarone (82)</b>	Diltiazam and verapamil in combination with amiodarone increase the risk of bradycardia, AV block and myocardial depression.
<b>Cardiac glycosides/ amiodarone (51, 82, 102)</b>	Seven patients on steady maintenance digoxin treatment had their plasma digoxin concentrations raised by a mean of 69% after taking amiodarone (600 mg daily); four of these patients developed symptoms of digoxin toxicity. Amiodarone may displace tissue-bound digoxin or interfere with digoxin excretion. Sharper increases in digoxin levels (66–800%) have been observed in (102) children. This exaggerated effect was attributed to impaired renal clearance of digoxin due to the inhibition of its tubular secretion (this route of clearance being specially important in children).
<b>Diuretics/amiodarone</b>	Toxicity of amiodarone increased in the presence of hypokalaemia induced by diuretics, e.g. acetazolamide, loop diuretics and thiazides.
<b>H<sub>2</sub> receptor antagonists/ amiodarone</b>	Cimetidine increases the plasma levels of amiodarone.

## V. INTERACTIONS WITH DISOPYRAMIDE

<b>Anti-arrhythmics/ disopyramide (4, 5, 7, 9, 22, 38)</b>	Disopyramide increases the QT interval. There is therefore a risk of <i>torsade de pointes</i> if given with any other anti-arrhythmic which also increases the QT interval, e.g. flecainide, quinidine, procainamide, amiodarone, sotalol and bretylium.
<b>Antibacterials/ disopyramide (5, 82, 104)</b>	Plasma concentrations of disopyramide are reduced by rifampicin but increased by erythromycin with increased risk of disopyramide toxicity. Rifampicin markedly increased the metabolism of disopyramide (DIS) in patients; plasma levels and AUC of disopyramide decreased while those of mono-N-dealkydisopyramide (MND) increased and the ratio MND/DIS in 24-hr urine increased distinctly in all subjects studied. During rifampicin treatment the mean

<i>Combination</i>	<i>Interaction</i>
	plasma levels of disopyramide did not reach the predicted therapeutic range (2–5 ng/ml, although the disopyramide doses used were loading doses generally recommended. The renal clearance of disopyramide declined after rifampicin (104).
<b>Anticonvulsants/ disopyramide (5)</b>	Plasma concentrations of disopyramide are reduced by anticonvulsants which induce cytochrome P450, e.g. phenobarbitone, phenytoin and primidone. Phenytoin markedly increased the metabolism of disopyramide in one epileptic patient and in two normal subjects (the effect subsided in 2 weeks after stopping phenytoin). Plasma levels and AUC of disopyramide decreased whilst those of its major metabolite, mono- <i>N</i> -dealkyldisopyramide, increased (11). An additional report of two patients showing a decrease in disopyramide serum concentration when phenytoin was given concurrently confirms this interaction which is likely to be due to enzyme induction of hepatic metabolism of disopyramide (105).
<b>Antihistamines/ disopyramide (5, 29, 30, 34, 82)</b>	Astemizole and tefenadine increase the QT interval. In combination with disopyramide which also increases the QT interval there is a risk of <i>torsade de pointes</i> .
<b>Antimalarial agents/disopyramide (23, 24, 31, 82)</b>	Disopyramide increases the QT interval. The risk of <i>torsade de pointes</i> is increased if disopyramide is used in combination with antimalarials which also increase QT interval, e.g. halofantrine, mefloquine, quinine.
<b>Antipsychotic agents/disopyramide (5, 20, 35, 36, 37)</b>	Phenothiazines, tri- and tetracyclic antidepressants, pimozide and haloperidol all increase the QT interval and if given in combination with disopyramide carry a risk of causing <i>torsade de pointes</i> .
<b>Diuretics/ disopyramide (82)</b>	Disopyramide toxicity is increased if diuretic-induced hypokalaemia occurs.

## VI. INTERACTIONS WITH LIGNOCAINE

<i>Combination</i>	<i>Interaction</i>
<b>Anti-arrhythmic agents/lignocaine (82)</b>	When used in combination with other anti-arrhythmic agents there is increased risk of myocardial depression.
<b><math>\beta</math>-Adrenergic blockers/lignocaine (106–108)</b>	The use of lignocaine (lidocaine) is complicated by its narrow therapeutic index; co-administration of propranolol reduces its metabolic clearance. There is therefore increased risk of myocardial depression.
<b>Cimetidine/lignocaine (109–111)</b>	<p>Cimetidine inhibits the metabolism of lignocaine and increases the risk of toxicity.</p> <p>Cimetidine (300 mg qid for 1 day) given to six normal subjects reduced the systemic clearance of lignocaine (lidocaine) (1 mg/kg per 10 min i.v. infusion) from 766 to 47 ml/min; the apparent volume of distribution at steady state and the degree of plasma protein binding of lignocaine were also decreased. Five of the six subjects noted lignocaine toxicity during the cimetidine infusion when peak lignocaine concentration was raised by a mean of 50%. A further study of the effect of cimetidine 300 mg four times a day on serum lignocaine levels in 15 patients undergoing lignocaine infusions of 1 mg/kg per min to 3 mg/kg per min confirmed substantial rises in serum lignocaine. Of the 15 patients who received lignocaine and cimetidine, six had lignocaine concentrations in the toxic range (over 5 ng/ml), two becoming lethargic and confused (at levels over 10 mg/ml).</p> <p>The mechanism of this interaction appears to be multifactorial, involving both altered distribution and clearance; these are likely to be due to cimetidine's known inhibition of oxidative pathways of biotransformation causing impaired metabolism of lignocaine and a decrease in liver blood flow via its vasoconstrictor effects on splanchnic circulation.</p> <p>Side effects should be anticipated when i.v. lignocaine is given to patients also receiving cimetidine. The total dose of lignocaine should be infused slowly or given by repeated small doses. Another report (110) cautions against routine administration of cimetidine to patients</p>

<i>Combination</i>	<i>Interaction</i>
<b>Nitrates and Prenylamine/ lignocaine (112)</b>	receiving lignocaine unless lignocaine levels are monitored.
<b>Smoking/lignocaine (113)</b>	Two elderly patients treated with sublingual nitrates and prenylamine (now withdrawn from the market) for stable angina suffered several episodes of syncope. Both showed a prolonged QT interval with premature ventricular beats and <i>torsade de pointes</i> type of ventricular tachycardia. The male patient showed sinus rhythm while the female had sinus bradycardia. After bolus doses of lignocaine (male, 100 mg; female, 50 mg) both experienced AV block. Pacemakers were inserted 3–5 days after withdrawal of prenylamine; the QT interval returned to normal and ventricular arrhythmias ceased. In two other patients with prenylamine-induced tachycardia, lignocaine neither precipitated AV block nor stopped the arrhythmias which were treated by pacemaker overdrive suppression. AV block after i.v. lignocaine is rare but it is possible that prenylamine and lignocaine may interact to cause AV conduction delays.
<b>Anti-arrhythmics/ mexiletine (82)</b>	Smokers had a significantly lower plasma-free fraction of lignocaine than non-smokers (mean, 0.258 vs. 0.307). This 19% increase in protein binding of lidocaine in smokers may be due to their higher concentrations of $\alpha_1$ -acid glycoprotein. Lignocaine has a narrow therapeutic index and smoking may negate its therapeutic effect.
<b>Antibacterials/ mexiletine (82)</b>	Rifampicin accelerates mexiletine metabolism.
<b>Anticonvulsants/ mexiletine (114)</b>	Phenytoin accelerates mexiletine metabolism. Unexpectedly low plasma concentrations of mexiletine were observed in three patients treated with mexiletine and concurrently taking phenytoin. A subsequent study

<i>Combination</i>	<i>Interaction</i>
<b>Anticonvulsants/ mexiletine cont.</b>	in 6 normal subjects given a single oral dose of mexiletine (400 mg) before and after 1 week of phenytoin (300 mg/day) showed that the mean half-life of elimination of mexiletine decreased from 17.2 to 8.4 hr; the mean AUC decreased from 17.67 to 6.21 ng/ml/hr. This enhanced clearance of mexiletine is likely to be due to induction of hepatic cytochrome P450 isoenzymes.
<b>Diuretics/mexiletine (82)</b>	Actions of mexiletine were antagonized in the presence of diuretic-induced hypokalaemia.
<b>Lignocaine and Procainamide/ mexiletine (97)</b>	Concomitant intravenous administration of lignocaine or procainamide is not recommended by the manufacturer.
<b>Theophylline/ mexiletine (82)</b>	Mexiletine increases the plasma level of theophylline
<b>VIII. INTERACTIONS WITH PROCAINAMIDE</b>	
<b>Alcohol/procainamide (115)</b>	Alcohol (ethanol) 2 hr before or 1.5 hr after oral procainamide (10 mg/kg) in normal subjects reduced the half-life and increased total body clearance and acetylation rate of procainamide. Alcohol caused greater enhancement of the total clearance in the slow than in the rapid acetylators. The mechanism of this interaction is not clear but it is likely to be due to increased formation of acetyl-CoA originating from acetate produced during ethanol metabolism, or to hepatic concentration of acetyl-CoA.
<b>Antacids/ procainamide (117)</b>	Antacids reduce the bioavailability of procainamide.
<b>Antihypertensive agents/procainamide (116–118)</b>	Additive hypotensive effects may occur; this is most likely with intravenous (i.v.) or intramuscular (i.m.) procainamide which can produce hypotensive effects when given alone. This interaction is seen very infrequently with oral procainamide (116). If procainamide is given i.v. or i.m. the progress of

<i>Combination</i>	<i>Interaction</i>
<b>Anti-arrhythmic agents/procainamide (4, 5, 7, 9, 22, 82)</b>	<p>patients receiving antihypertensive therapy should be carefully monitored for possible additive hypotensive effects.</p> <p>Severe hypotension may be treated by placing the patient in the supine position with the feet raised. If necessary an iv infusion of noradrenaline acid tartrate (8 ng/ml in sodium chloride injection) may be started (117) or adrenaline (118).</p>
<b>Antibacterials/ procainamide (82, 119, 120)</b>	<p>Amiodarone increases procainamide plasma concentration. Procainamide increases QT interval and should not be used with any other anti-arrhythmic, which has the same action, e.g. flecainide, quinidine, disopyramide, sotalol or bretylium.</p> <p>A single case has been reported in which neurological side effects (hallucination and delirium) followed the combined use of procainamide and lignocaine.</p>
<b>Antihistamines/ procainamide (7, 29, 30, 34)</b>	<p>Trimethoprim increases the plasma levels of procainamide (82).</p> <p>The antibacterial action of sulphonamides is antagonized by <i>p</i>-aminobenzoic acid and compounds derived from it, especially procaine and related compounds (which include procainamide).</p> <p>Procainamide potentiates the neuromuscular blocking action of aminoglycoside antibiotics (119, 120).</p>
<b>Antimalarials/ procainamide (23, 24, 31)</b>	<p>There is an increased risk of ventricular arrhythmias and <i>torsade de pointes</i> when procainamide is given concomitantly with astemizole or terfenadine, since these drugs, like procainamide, increase the QT interval.</p>
<b>Cimetidine/ procainamide (82, 121, 122, 123)</b>	<p>Halofantrine and other antimalarial agents increase the QT interval as does procainamide. Given concomitantly there is an increased risk of ventricular arrhythmias including <i>torsade de pointes</i>.</p> <p>Cimetidine increases procainamide plasma concentrations by reducing the renal clearance of procainamide.</p> <p>Pharmacokinetic studies in six normal subjects showed</p>

*Combination**Interaction***Cimetidine/  
procainamide cont.**

that cimetidine (1000 mg on 1 day) concurrently with procainamide (1 g orally as a single dose) increased the AUC of procainamide plasma concentration by an average of 35%. Mean elimination half-life of procainamide was prolonged from 2.9 to 3.8 hr. The interaction was not due to inhibition of procainamide metabolism but to a 50% reduction in renal clearance (347 reduced to 196 ml/min), which was presumably due to cimetidine-induced reduction in renal blood flow, or competition for active tubular secretion, or both. Procainamide has a narrow therapeutic index and caution is warranted when using it in patients also receiving cimetidine, especially in the elderly who have a reduced ability to clear both drugs (122, 123). Dosage modification may be necessary.

**Cholinergic  
drugs/procainamide**

Procainamide has anticholinergic properties and may reduce the effect of drugs used in the treatment of myasthenia gravis and possibly also those used in glaucoma.

*Note: Quinidine also has anticholinergic properties.*

**Skeletal muscle  
relaxants/  
procainamide  
(82, 119)**

Neuromuscular blocking action may be enhanced by procainamide; recurarization is possible during recovery from neuromuscular blockade.

*Note: Quinidine also potentiates muscle relaxant drugs and may cause recurarization.*

**IX. DRUG INTERACTIONS WITH PROPAFENONE****Anti-arrhythmics/  
propafenone (11, 20)**

Quinidine increases the plasma concentration of propafenone.

Increased myocardial depression when given concomitantly with any anti-arrhythmic.

**Antibacterials/  
propafenone (11)**

Rifampicin reduces plasma concentration of propafenone.

**Anticoagulants/  
propafenone (11)**

Propafenone increases the anticoagulant effect of warfarin and nicoumalone.

<i>Combination</i>	<i>Interaction</i>
<b>Antihistamines/ propafenone (20)</b>	Increased risk of ventricular arrhythmias with astemizole and terfenadine, both of which increase QT interval.
<b><math>\beta</math>-adrenergic blockers/ propafenone (11)</b>	Propafenone when given concomitantly with either metoprolol or propranolol causes increased plasma concentration of these drugs.
<b>Cardiac glycosides/ propafenone (11)</b>	Propafenone increases plasma concentration of digoxin
<b>Cimetidine/ propafenone (11)</b>	Cimetidine leads to increased plasma propafenone levels
<b>Cholinergics/ propafenone (82)</b>	Propafenone has been reported to antagonize the effects of neostigmine and pyridostigmine
<b>Ketoconazole/ propafenone (147)</b>	This combination has been reported to result in generalized seizures.
<b>Theophylline/ propafenone (82)</b>	Propafenone when given in combination with theophylline leads to increased plasma theophylline levels.

## X. DRUG INTERACTIONS WITH QUINIDINE

<b>Amiloride/quinidine (148)</b>	This combination has been reported to lead to an exaggeration of the effects of quinidine on the QRS complex. Amiloride can prolong the QT interval in its own right.
<b>Amiodarone/ quinidine (103)</b>	Two patients treated with a combination of amiodarone and quinidine for minor arrhythmia both developed dangerous atypical ventricular tachycardia ( <i>torsade de pointes</i> ). Both patients had QT-interval prolongation. A combination of amiodarone and quinidine given to normal subjects raised the plasma quinidine concentration and prolonged the QT-interval, confirming the observation of a clinically important and potentially dangerous interaction between the two drugs.

<i>Combination</i>	<i>Interaction</i>
<b>Antacids/quinidine</b>	Reduced excretion of quinidine takes place in alkaline urine. Plasma quinidine levels may be increased.
<b>Anti-arrhythmic agents/quinidine (20)</b>	Quinidine increases QT interval and should not be used with any other anti-arrhythmic agent which has this effect.
<b>Antibacterial agents/quinidine (124, 125, 149)</b>	Rifampicin increases rate of quinidine metabolism. The significance of this interaction can be judged from the following case histories. Ventricular dysrhythmia responded to treatment with quinidine but the patient relapsed when rifampicin was started to treat co-existing tuberculosis (124). Pharmacokinetic studies in normal subjects showed that the mean elimination half-life of oral quinidine was reduced by rifampicin (6.1–2.3 hr). The mean AUC fell from 15.5 to 2.6 ng/ml/min/kg. Corresponding data for i.v. quinidine were a reduction from 6.6 to 2.1 hr and 10.3 to 5.2 ng/ml/min/kg, respectively (125). Addition or discontinuation of rifampicin may have serious implications for patients receiving quinidine. Erythromycin has been reported to increase quinidine blood levels (149).
<b>Anticoagulants/quinidine (126–128)</b>	Anticoagulant effects of warfarin and nicoumalone are enhanced.
<b>Anticholinergic agents/quinidine (129)</b>	Quinidine has vagal blocking properties and exerts additive vagolytic effects in the presence of anticholinergic drugs (129). Caution should be observed in giving quinidine and anticholinergic drugs concomitantly; many antisecretory, spasmolytic and anti-Parkinsonian drugs have predominant anticholinergic properties, as also have anti-emetic agents and mydriatics.

<i>Combination</i>	<i>Interaction</i>
<b>Anticonvulsants/ quinidine</b> (29, 30, 34)	Phenobarbitone, phenytoin and primidone increase the rate of metabolism of quinidine and reduce its effect.
<b>Antihistamines/ quinidine</b> (29, 30, 34)	Astemizole and terfenadine increase the QT interval as does quinidine. Given concomitantly there is an increased risk of ventricular arrhythmias and <i>torsade de pointes</i> .
<b>Antihypertensive agents/quinidine</b> (129, 130)	Quinidine reduces blood pressure, primarily due to peripheral vasodilation; it may also cause a precipitous fall in blood pressure as part of a hypersensitivity reaction. Thus, additive hypotensive effects may occur when quinidine is given concomitantly with antihypertensive therapy. Patients stabilized on antihypertensive drugs should be carefully monitored if quinidine is given parenterally or in high oral dosage. Additive hypotensive effects may occur.
<b>Antimalarials agents/quinidine</b> (22, 23, 24, 31)	A number of antimalarials, e.g. halofantrine increase the QT interval and, when taken in combination with quinidine, can induce ventricular arrhythmias and <i>torsade de pointes</i> .
<b>Antipsychotic agents/quinidine</b> (22, 39)	Phenothiazines, tri- and tetracyclic drugs primazide and haloperidol like quinidine increase the QT interval. When administered concomitantly there is increased risk of ventricular arrhythmias and <i>torsade de pointes</i> .
<b>Calcium channel blockers/quinidine</b>	Nifedipine reduces plasma quinidine concentrations. Verapamil increases plasma quinidine concentrations. There is a risk of serious hypotension.
<b>Cardiac glycosides/quinidine</b> digoxin/quinidine (52–64)	Quinidine causes an increase in serum digoxin concentration in 90% of cases; increase is variable but averages two-fold and the raised levels are maintained as long as quinidine is co-administered (52). Mechanism of interaction suggested is displacement of digoxin from tissue binding sites (57, 58), thus reducing its distribution volume (54, 59), and this is followed by decreased renal clearance of digoxin

<i>Combination</i>	<i>Interaction</i>
<b>Cardiac glycosides/quinidine</b> digoxin/quinidine <i>cont.</i>	(52–54, 58, 60) which is saturable (68), and this is the determinant of the serum level during the steady state (59). The underlying mechanisms are a quinidine-induced reduction of both renal and non-renal clearance of digoxin, and a quinidine-induced redistribution of digoxin from tissue binding sites (57–58), notably a reduction in the ratio of skeletal muscle to serum digoxin levels. This is suggestive of a reduced binding of digoxin in muscle (61–64).
digitoxin/quinidine (70–74)	Although it is well established that a digoxin–quinidine interaction increases plasma digoxin levels, a corresponding interaction between digitoxin and quinidine is still somewhat controversial. A random cross-over study in 10 normal subjects showed that the two drugs could be taken together without evoking change in digitoxin kinetics. These negative findings have been questioned and other studies have shown that digitoxin serum levels increased after starting quinidine.
<b>Cholinergic drugs/quinidine</b> (129)	Quinidine has anticholinergic properties and may reduce the effects of drugs used in the treatment of myasthenia gravis and possibly also those used in glaucoma. The progress of patients on cholinergic drugs should be carefully checked if quinidine is given. In particular, quinidine may antagonize the effects of neostigmine and edrophonium in the treatment of myasthenia gravis. <i>Note: Procainamide also has anticholinergic properties.</i>
<b>Diuretics/quinidine</b> (131–134)	Acetazolamide reduces the renal excretion of quinidine, as also do thiazide diuretics. These diuretics tend to make the urine alkaline; this results in an increased proportion of un-ionized quinidine. Renal tubular reabsorption of quinidine is thus increased and serum levels may rise, thereby increasing the risk of side effects and toxicity. In addition, thiazides and parenteral quinidine may exhibit additive hypotensive effects.

<i>Combination</i>	<i>Interaction</i>
<b>Cimetidine/quinidine</b> (82, 135)	Care should always be used in prescribing urine alkalinizing agents (this includes sodium bicarbonate) for patients receiving quinidine. Quinidine toxicity is enhanced in the presence of diuretic-induced hypokalaemia.
<b>Propranolol/quinidine</b> (136–137)	Cimetidine inhibits quinidine metabolism. Antacids, not cimetidine, may be the preferred choice in acutely ill patients who are receiving concurrent treatment with cardio-active drugs.
<b>Skeletal muscle relaxants/quinidine</b> (138, 139, 140)	Both quinidine and propranolol have a negative ionotropic action on the heart.
	Quinidine administration to patients recovering from the effects of tubocurarine leads to recurarization and apnoea. Quinidine potentiates both depolarizing and non-depolarizing (curare-like) muscle relaxants. Avoid the use of quinidine pre- and postoperatively. Neostigmine does not reverse this blockade. <i>Note: Procainamide cannot be substituted since a similar interaction may occur.</i>
<b>Sucralfate/quinidine</b> (145)	Reduced absorption of both digoxin and quinidine with markedly below expected levels of both in a 71-year-old woman lead to atrial flutter, rapid ventricular response and chest pain.
<b>Timolol eye drops/quinidine</b> (146)	Timolol eye drops have been reported in combination with quinidine to have enhanced the negative ionotropic action of quinidine on the heart.

## XI. INTERACTIONS WITH VERAPAMIL

(see also section on antihypertensive drugs)

<i>Combination</i>	<i>Interaction</i>
<b>Calcium adipate and calciferol/verapamil</b> (141)	Atrial fibrillation reappeared after 1 week's dosage with calcium adipinate (1.2 g/day) and calciferol (3000 IU/day) in an elderly patient successfully treated with verapamil for atrial fibrillation of long duration. The

<i>Combination</i>	<i>Interaction</i>
<b>Calcium adipate and calciferol/verapamil <i>cont.</i></b>	patient reconverted to sinus rhythm after i.v. verapamil, fluids and frusemide. Verapamil inhibits the transmembranal influx of calcium into cardiac cells and the release of calcium from the endoplasmic reticulum causing a negative inotropic effect. This effect was reversed in this case by the increase in extracellular concentration of calcium.
<b>Clonidine/verapamil (143)</b>	The combination of clonidine with verapamil has lead to AV block and severe hypotension.
<b>Digoxin/verapamil (86, 87, 88)</b>	In normal subjects verapamil significantly decreased the mean volume of distribution of digoxin from 0.83 to 0.64 l/kg, and digoxin total body clearance from 3.28 to 2.15 ml/min/kg; both renal and extrarenal clearance were impaired. Verapamil may inhibit renal clearance of digoxin by inhibiting tubular secretion. Mean elimination half-life of digoxin increased by 31% (76). Significant increases in digoxin serum concentrations (0.76 to 1.31 ng/ml) have also been reported following the use of verapamil (240 mg daily) in 49 patients who were previously stabilized on digoxin; symptoms of toxicity occurred in several patients (77). Frequent plasma digoxin measurements and adequate digoxin dosage reduction are recommended to avoid unnecessary risks during the combined use of digoxin and verapamil (76-78).
<b>Glibenclamide/ verapamil (142)</b>	Verapamil (120 mg orally) has been shown to increase the plasma levels of glibenclamide (5 mg orally) in nine male volunteers. The area under the time-plasma concentration curve was increased by about 25%. In the male volunteers tested there was no effect on plasma glucose or insulin.
<b>Metoprolol/verapamil (144)</b>	This combination has been reported to have resulted in cardiogenic shock and complete heart block
<b>Rifampicin/verapamil (143)</b>	Rifampicin increases the hepatic metabolism of verapamil. Normal doses of verapamil are unlikely to give

*Combination**Interaction*

therapeutically effective plasma levels in patients taking rifampicin.

### **Recommended further reading**

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## **2.2. INTERACTIONS WITH DRUGS USED TO TREAT HYPERTENSION**

A wide variety of active substances with an equally wide number of primary pharmacological effects have been and are used to treat hypertension. This chapter has therefore been divided into a number of sections dealing with each of the various categories of antihypertensive agent and their interactions according to the primary pharmacological action of that class of agent. The order in which the therapeutic groups are presented has been determined by the current volume of clinical use of these categories.

### **1. $\beta$ -ADRENERGIC BLOCKING DRUGS**

#### **Group 1.**

##### **Cardioselective $\beta$ -adrenergic blocking agents**

Acebutolol  
Atenolol  
Betaxolol  
Bisoprolol  
Esmalol  
Metoprolol

#### **Group 2.**

##### **Non-cardioselective $\beta$ -adrenergic blocking agents**

Alprenolol hydrochloride  
Bufuralol hydrochloride  
Bunitrolol  
Bupranolol hydrochloride  
Nadolol  
Oxprenolol  
Pindolol  
Propranolol  
Sotalol\*  
Timolol  
Toliprolol

#### **Group 3.**

##### **Combined $\alpha$ - and $\beta$ -adrenergic blocking agents**

Labetalol hydrochloride

\***Sotalol** prolongs QT interval and should not be administered with other drugs that prolong QT interval. There is increased risk of ventricular arrhythmias and *torsade de pointes*.

### Interactions with $\beta$ -adrenergic blocking agents

<i>Combination</i>	<i>Interaction</i>
<b>Anti-arrhythmic agents/<math>\beta</math>-adrenergic blocking drugs</b>	
<b>Amiodarone/<math>\beta</math>- adrenergic blocking agent (1)</b>	Increased risk of myocardial depression and severe bradycardia and AV block
<b>Calcium channel blockers/<math>\beta</math>-adrenergic blocking agents (1)</b>	The combined use of $\beta$ -adrenocaptor blocking drugs with calcium channel blocking agents with negative ionotropic effects such as verapamil or diltiazam can lead to exaggeration of these ionotropic effects, particularly in patients with impaired ventricular function and/or sinuatrial or atrial ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the $\beta$ -adrenoceptor blocking drug nor the calcium channel blocker should be administered within 48 hr of discontinuing the other, concomitant therapy with dihydropyridines. Calcium channel blockers, such as nifedipine, may increase the risk of hypotension and cardiac failure.
<b>Nifedipine/atenolol (2-6)</b>	A case report has shown that the combination of nifedipine and a $\beta$ -blocker (atenolol) may cause cardiac failure in patients with angina (2). This confirms an earlier report of two cases of the same interaction (3). Nifedipine and $\beta$ -blockade have also been implicated in causing severe hypotension (4, 5). The mechanism of these interactions is that increased cardiac sympathetic activity compensates for the negative inotropic effect of nifedipine, but this is prevented by $\beta$ -blockade (6).
<b>Digitalis/propranolol (7, 8)</b>	Propranolol is used with digitalis to reduce the ventricular rate in auricular fibrillation and flutter which are not effectively controlled by digitalis alone (7). Propranolol is also usually effective in controlling arrhythmias associated with digitalis intoxication (7), but may potentiate digitalis bradycardia (8). These

<i>Combination</i>	<i>Interaction</i>
<b>Disopyramide/ propranolol, atenolol, etc. (1, 9)</b>	uses are due to the drug's membrane-stabilizing actions rather than to its $\beta$ -adrenergic blocking action.
<b>Lidocaine/propranolol (10)</b>	The propranolol data sheet extends the caution of co-administration to all $\beta$ -blockers and all class I anti-arrhythmic agents. After 1 week treatment with atenolol (100 mg daily by mouth) the mean clearance of disopyramide in six patients with cardiac ischaemia and in three normal volunteers decreased by almost 20%. This modest reduction in the clearance of disopyramide may be sufficient to exaggerate the pharmacodynamic interaction between disopyramide and $\beta$ -blocking drugs.
<b>Lignocaine/ propranolol (1, 11)</b>	The use of lidocaine (lignocaine) is complicated by its narrow therapeutic index; co-administration of propranolol reduces its metabolic clearance during prolonged infusion and this will increase the likelihood of toxicity. Two cases of this interaction evoking lidocaine toxicity have been reported.
<b>Procainamide/ propranolol (12)</b>	Increased risk of lignocaine toxicity when given in conjunction with propranolol, since the plasma concentration of lignocaine rises by 30% or more.
<b>Anaesthetic agents/ <math>\beta</math>-adrenergic agents 1, 11)</b>	Elimination half-life was increased and plasma clearance of procainamide was decreased in normal subjects receiving long-term administration of propranolol as compared with controls. The clinical significance of this interaction is unknown but it may be important due to the common use of the two drugs.
<b>Antibiotics, rifampicin/ <math>\beta</math>-adrenergic blocking agents (13)</b>	There is enhanced risk of hypotension when patients on $\beta$ -adrenergic blocking drugs are anaesthetized. The use of $\beta$ -adrenergic blocking drugs with anaesthetic agents results in the attenuation of reflex tachycardia in response to hypotension.
	Rifampicin (600 mg at night) for 15 days reduced the AUC of metoprolol (single oral dose 100 mg) in normal subjects but did not change the rate constant for elimination from plasma. This change in kinetics of

<i>Combination</i>	<i>Interaction</i>
<b>Antibiotics, rifampicin/ β-adrenergic blocking agents cont.</b>	metoprolol is likely to be due to induction of hepatic microsomal enzymes by rifampicin, since in the same study rifampicin also reduced the AUC and increased the elimination rate constant for antipyrine, an indicator of hepatic mixed-oxidase activity. Some loss of β-blockade should be anticipated if rifampicin is given to patients who receive metoprolol.
<b>Antidepressants (MAOIs)/ β-adrenergic blocking agents (16)</b>	The use of MAOIs with β-adrenergic blocking agents is contraindicated, since a severe hypertensive crisis may be precipitated because of unopposed α-adrenergic activity in patients receiving sympathomimetic amines.
<b>Antidepressants (fluvoxamine)/ propanolol</b>	The SSRI fluvoxamine inhibits propranolol metabolism and increases risk of severe hypotension.
<b>Antidiabetic agents/ β-adrenergic blocking agents (11, 19, 20, 22, 23)</b>	Propranolol enhances the hypoglycaemic effect of antidiabetic agents and masks the warning signs of hypoglycaemia, e.g. tremor sweating. β-adrenergic blockade reduces the rise in blood sugar to adrenaline. Propranolol blunts the rebound of blood sugar following insulin-induced hypoglycaemia; it also blocks the clinical signs of hypoglycaemia, such as sweating and trembling, by which patients and/or relatives recognise hypoglycaemic episodes. However, cardioselective β-blockade with metoprolol reduced blood pressure satisfactorily in a group of insulin-dependent diabetics. No influence was observed on parameters reflecting diabetic control; patients able to recognize symptoms of insulin-induced hypoglycaemia maintained this ability during metoprolol treatment (19). Other studies in non-insulin-dependent diabetics have also indicated that the use of a selective β-blocker (acebutolol) has advantages over a non-selective blocker (propranolol) (20). Use this combination (propranolol/insulin) with caution; dosage of insulin may have to be reduced by 20% if β-adrenergic blockade is required. This caution

<i>Combination</i>	<i>Interaction</i>
<b>Antihistamines/ β-adrenergic blocking agents (sotalol) (11, 15)</b>	does not appear to apply if cardioselective β-blockers are used (e.g. acebutolol, metoprolol).
<b>Antihistamines/H<sub>2</sub> receptor blockers/ β-adrenergic blocking agents (11, 18)</b>	The risk of ventricular arrhythmias due to prolongation of the QT interval associated with sotalol is potentiated by the non-sedative antihistamines astemizole and terfenidine, there is a risk of <i>torsade de pointes</i> .
<b>Antihypertensive agents/β-adrenergic blocking agents (clonidine) (11)</b>	Plasma concentrations of propranolol and labetalol increased by cimetidine.
<b>Antimalarials/ β-adrenergic blocking agents (11, 14, 15)</b>	Both propranolol and cimetidine have been reported to cause male impotence. This effect may be potentiated when co-administered. β-Adrenergic blocking agents exacerbate rebound hypertension which can follow the withdrawal of clonidine. If the two agents are administered together for the control of hypertension the β-adrenergic blocking drug should be withdrawn several days before the subsequent withdrawal of clonidine.
<b>Antipsychotic agents/β- adrenergic blocking agents (11, 14, 15)</b>	Risk of ventricular arrhythmias associated with sotalol potentiated by halofantrine, due to prolongation of QT interval. Increased risk of bradycardia with mefloquine.
<b>Antithyroid drugs/propranolol (11, 17)</b>	Risk of ventricular arrhythmias associated with sotalol increased by phenothiazines, and tricyclic antidepressants due to prolongation of QT interval.
	Plasma propranolol steady-state concentrations increased significantly after correction of thyroid disorder in hyperthyroid patients by surgery, antithyroid drugs or radio-iodine. Thyroxine increases the rate of metabolism of propranolol and other β-adrenergic blockers. Propranolol may be used to control hyperthyroid tremor, and when the hyperthyroidism is corrected

<i>Combination</i>	<i>Interaction</i>
<b>Antithyroid drugs/propranolol</b> <i>Cont.</i>	there may be unexpected and a severe hypotensive episode.
<b>Diuretics/ β-adrenergic blocking agents (11)</b>	Enhanced hypotensive effect when thiazides and $\beta$ -adrenergic blockers are co-administered. Increased risk of ventricular arrhythmias due to prolongation of QT interval with sotalol in presence of diuretic induced $K^+$ depletion.
<b>Ergot alkaloids/ β-adrenergic blocking agents (1, 11)</b>	Caution must be exercised if ergotamine, dihydroergotamine or other ergot alkaloids are given at the same time as propranolol or other $\beta$ -adrenergic blockers since severe peripheral vasospastic reactions have been reported with risk of loss of digits.
<b>Non-steroidal anti-inflammatory agents/β-adrenergic blocking agents (1)</b>	Concomitant use of prostaglandin synthetase inhibiting NSAIDs such as ibuprofen, indomethacin, etc., decreases the hypotensive effect of propranolol.
<b>Sex hormones/ β-adrenergic blocking agents (1, 11)</b>	Oestrogens, combined oral contraceptives and HRT antagonize the hypotensive effect of $\beta$ -adrenergic blocking drugs.
<b>Skeletal muscle relaxants/ β-adrenergic blockers (1)</b>	Propranolol potentiates the muscle relaxant effect of these agents. Use of $\beta$ -adrenergic receptor blocking drugs with anaesthetic agents may result in the attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents that depress myocardial function should be avoided.
<b>Sympathomimetic amines/β-adrenergic blocking agents (11)</b>	Severe hypertension with adrenaline and noradrenaline especially with non selective $\beta$ -blockers occurs due to unopposed $\alpha$ -adrenergic effects. Severe hypertension has also been reported with sympathomimetic amines in anorectic, cough and cold remedies being taken by patients receiving $\beta$ -adrenergic blocking drugs.

## 2. ANGIOTENSIN CONVERTING-ENZYME (ACE) INHIBITORS

<b>Captopril</b>	available as 12.5-, 25.0- and 50.0-mg tablets and 50 mg in combination with 25 mg hydrochlorthiazide
<b>Cilazapril</b>	available as 250-, 500- and 1.0-, 2.5- and 5.0-mg tablets
<b>Enalapril maleate</b>	available as 2.5-, 5.0-, 10.0- and 20.0-mg tablets and 20.0 mg enalapril in combination with 12.5 mg hydrochlorthiazide
<b>Fasinopril</b>	available as 10.0- and 20.0-mg tablets
<b>Lisinopril</b>	available as 2.5-, 5.0-, 10.0- and 20.0-mg tablets and 10 mg in combination with 12.5 mg hydrochlorthiazide
<b>Perindopril</b>	available as 2.0- and 4.0-mg tablets
<b>Quinapril</b>	available as 5.0-, 10.0- and 20.0-mg tablets and 10 mg in combination with 12.5 mg hydrochlorthiazide
<b>Ramipril</b>	available as 1.25-, 2.5- and 5.0-mg capsules
<b>Trandolapril</b>	available as 0.5-, 1.0- and 2.0-mg capsules

### Extent of clinical use

ACE inhibitor-containing preparations in 1994 represented a cost to the British NHS of over £1160 million or 4.15% of the total FHSA medicines expenditure.

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### Therapeutic class and uses

Angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II. ACE inhibitors are well tolerated and are used widely in the treatment of hypertension and heart failure.

Angiotensin converting enzyme (ACE) inhibitors are lipophilic prodrug esters which are converted to active hydrophilic diacid metabolites, e.g. enalapril to enalaprilat and perindopril to perindoprilat.

The relationship between the dose of ACE inhibitor and the subsequent blood pressure reduction is complex. ACE inhibitors interact with both circulating and local renin-angiotensin systems and alter the concentration of the pressor peptide angiotensin II. MacFadyen *et al.* (99) described a qualitative difference between the blood pressure responses of captopril, enalapril and perindopril in a group of 72 patients with stable heart failure aged 59–82 years. This patient group is acknowledged to be at risk from significant hypotensive responses following ACE inhibitor therapy, which may in part be due to activation of the renin–angiotensin system. Parallel groups of patients were given placebo 6.25 mg captopril, 2.5 mg enalapril or 2.0 mg perindopril orally or a constant rate intravenous infusion of placebo, 1.5 mg enalaprilat or 1.0 mg perindoprilat.

The maximum recorded fall in mean arterial blood pressure was significantly greater than placebo ( $-16 \pm 7.7$  mmHg) for captopril ( $-22 \pm 12$ ) and enalapril ( $-26 \pm 8$ ) but not perindopril ( $-15 \pm 8$ ). Enalapril reduced the heart rate ( $-11 \pm 7$  beats/min) compared to placebo (4–8 hr) and perindopril (20 min to 10 hr). The different blood pressure responses for perindopril and enalapril were observed with similar mean maximal ACE inhibition (perindopril,  $68 \pm 14\%$ ; enalapril,  $63 \pm 12\%$ ). In contrast, the mean maximal fall in mean arterial pressure was similar for both enalaprilat ( $-27 \pm 10$  mmHg) and perindoprilat ( $-24 \pm 10$  mmHg).

Plasma concentrations of ester prodrugs peaked early but persisted during the study (enalapril,  $43 \pm 21$  ng/ml at  $1.95 \pm 0.7$  hr; perindopril,  $38 \pm 24$  ng/ml at  $1.74 \pm 0.7$  hr). This was followed by the appearance of enalaprilat ( $11.7 \pm 5.4$  ng/ml) and perindoprilat ( $4.8 \pm 2.5$  ng/ml) after desterification, both showing sustained plateau concentrations.

Earlier *in vitro* work by Harrigan *et al.* (100) has suggested that perindopril may significantly attenuate the inhibition of ACE by perindoprilat in plasma. This does not appear to be the case for enalapril and enalaprilat. First-dose hypotensive effects in patients with congestive heart failure could possibly be avoided or reduced due to this interaction between prodrug and active metabolite.

An increase in the dose of perindopril or continuing therapy would be likely to overcome this concentration-dependent effect. This interaction between drug and metabolite could therefore be beneficial.

Food has been shown to reduce the bioavailability of the angiotensin-converting enzyme inhibitor captopril, but not the bioavailability of inhibitors administered as ester prodrugs. Perindopril is the ester prodrug of the angiotensin-converting enzyme inhibitor perindoprilat. The influence of food on the pharmacokinetics of perindopril (4 mg administered orally) and the time course of angiotensin-converting enzyme inhibition in serum was studied in a randomized crossover short-term study of 12 healthy subjects by Lecocq *et al.* (101). Food significantly decreased the relative availability of perindoprilat by  $35 \pm 42\%$ , the fractional urinary excretion of perindoprilat from  $19 \pm 7$  to  $13 \pm 4\%$  ( $p < 0.05$ ), and the partial metabolic clearance of perindopril to perindoprilat from  $102 \pm 57$  to  $72 \pm 32$  ml/min ( $p < 0.05$ ). These changes were associated with significant decrease in the area under the percent angiotensin-converting enzyme inhibition-versus-time curve by 15% ( $p < 0.05$ ). Food did not alter the total amount of drug recovered in urine as perindopril and its metabolites, and it did not alter perindoprilat renal clearance. Lecocq *et al.* concluded that food alters the conversion of perindopril to its active metabolite perindoprilat after single-dose administration of perindopril.

### **Side effects**

The most common side effect with all ACE inhibitors is persistent dry cough. In a study on 1013 patients on ACE inhibitors the prevalence of cough was 12.3% and in the control group it was 2.7% (24). Voice changes, loss of taste and sore mouth have been reported. Rashes, angioneurotic oedema, hypotension, proteinuria, neu-

tropenia agranulocytosis, thrombocytopenia, renal impairment, increased liver enzyme levels, liver damage, cholestatic jaundice and pancreatitis have all been reported. However, other than cough, all reactions are uncommon and ACE inhibitors are well tolerated. It has been shown (25) that there is an enhanced dose-related sensitivity to inhaled capsaicin in patients taking ACE inhibitors. It was suggested that ACE inhibitors may alter the cough reflex in all patients, with those who develop a cough representing the extreme of this general shift.

Captopril, enalapril, lisinopril, perindopril and ramipril all appear to precipitate severe angioneurotic oedema in some patients, and appropriate warnings are given in the data sheets (26, 28, 30–32).

### **Drug interactions with ACE inhibitors**

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/ACE inhibitor</b> (11)	Enhanced hypotensive effect
<b>Allopurinol/ACE inhibitor</b> (26)	There have been reports of neutropenia and/or Stevens-Johnson syndrome in patients receiving concomitant allopurinol and captopril.
<b>Antipsychotic agents/ACE inhibitor</b> (11)	Enhanced hypotensive effect of ACE inhibitors by chlorpromazine.
<b>β-Adrenergic blocking drugs/ACE inhibitor</b> (11, 30)	Enhanced hypotensive effect of ACE inhibitors.
<b>Baclofen/ACE inhibitor</b> (27)	Enhances the hypotensive effect of ACE inhibitors.
<b>Calcium channel blocking agents/ACE inhibitor</b> (11)	Enhanced hypotensive effect.
<b>Carbenoxolone/ACE inhibitor</b> (29)	Carbenoxolone causes sodium retention and antagonizes hypotensive action of ACE inhibitors.

<i>Combination</i>	<i>Interaction</i>
<b>Clonidine/ACE inhibitor (26)</b>	The normal onset of the antihypertensive action of captopril is delayed when patients treated with clonidine are changed to captopril.
<b>Corticosteroids/ACE inhibitor (11)</b>	Antagonism of hypotensive effect of captopril.
<b>Dialysis membranes/ACE inhibitor (11)</b>	The Committee on Safety of Medicines in 1992 required all ACE inhibitors to carry a standard warning that anaphylactoid-like reactions during haemodialysis with high-flux dialysis membranes, e.g. AN69, might occur in patients on ACE inhibitors.
<b>Digoxin/ACE inhibitor (11)</b>	Plasma concentration of digoxin increased by captopril. Increased risk of digoxin-related side effects
<b>Diuretics/ACE inhibitor (11, 26)</b>	Diuretics potentiate the antihypertensive effect of captopril. Profound first-dose hypotension may occur when ACE inhibitors are introduced to patients with heart failure who are taking a loop diuretic, e.g. frusemide. Temporary withdrawal of the loop diuretic reduces the risk but may result in rebound pulmonary oedema. ACE inhibitors should therefore be started at low dosage and increased gradually in such patients. Since captopril reduces aldosterone production elevation of K <sup>+</sup> may occur. Potassium-sparing diuretics should not be used in conjunction with ACE inhibitors.
<b>Immunosuppressants/ ACE inhibitor (26)</b>	Azathioprine and cyclophosphamide have been associated with blood dyscrasias in patients with renal failure who were also taking captopril.
<b>Indomethacin/ACE inhibitor (11, 26, 30)</b>	A reduction in the antihypertensive effect of captopril may occur. This effect may also occur with other NSAIDs.
<b>Levodopa/ACE inhibitor (11)</b>	Levodopa increases the hypotensive action of captopril.

<i>Combination</i>	<i>Interaction</i>
<b>Lithium/ACE inhibitor</b> (11, 26, 30)	Concomitant use of captopril with lithium results in an increase in serum lithium levels by the same mechanism as captopril retains sodium. Increased risk of lithium toxicity.
<b>Oral contraceptives/ACE inhibitor</b> (11)	Oestrogens and combined oral contraceptives antagonize the hypotensive action of ACE inhibitors.
<b>Probenecid/ACE inhibitor</b> (26)	Probenecid reduces the renal clearance of captopril and thus enhances the hypotensive effect.
<b>Potassium salts/ACE inhibitor</b> (11)	Precipitates hyperkalaemia.
<b>Procainamide/ACE inhibitor</b> (26)	Concomitant use of captopril and procainamide is alleged to increase the risk of neutropenia and Stevens-Johnson syndrome.
<b>Vasodilators/ACE inhibitors</b> (26)	The hypotensive effect of captopril is enhanced when used in conjunction with peripheral vasodilators, e.g. minoxidil.
<b>Venom/ACE inhibitors</b> (28)	Patients receiving ACE inhibitors during desensitization with hymenoptera (bee or wasp) venom have experienced life-threatening anaphylactoid reactions. These reactions have been avoided by temporarily withholding ACE inhibitor therapy prior to each desensitization.

### 3. CALCIUM CHANNEL BLOCKERS

**Amlodipine besylate**  
**Diltiazem hydrochloride**  
**Felodipine**  
**Isradipine**  
**Lacidipine**  
**Nicardipine hydrochloride**  
**Nifedipine**  
**Nimodipine**  
**Verapamil hydrochloride**

Calcium channel blockers interfere with the inward movement of calcium ( $\text{Ca}^{2+}$ ) ions through the slow channels of active cell membranes. Calcium channel blockers influence contractile myocardial cells, cells in the conducting system of the heart, and the cells of vascular smooth muscle. This means that myocardial contractility may be reduced, conduction in the AV system depressed, and coronary and systemic vascular smooth muscle tone reduced leading to vasodilation. Calcium channel blockers should in general be avoided in patients with heart failure. Calcium channel blockers differ in their predilection for possible sites of action.

**Verapamil** reduces cardiac output, slows heart rate, and impairs AV conduction. It may precipitate heart failure and cause hypotension. **Verapamil** *should not be used with  $\beta$ -adrenergic blockers.*

**Diltiazem** has a degree of selectivity for dilating the coronary arteries and is used in the treatment of angina and hypertension. It has lesser propensity to produce a negative ionotropic effect than **verapamil**, however use of  $\beta$ -adrenergic blocking agents in combination with diltiazem is not advised.

The major group of calcium channel blockers the dihydropyridines also show varying degrees of selectivity.

**Nifedipine** relaxes vascular smooth muscle in coronary and peripheral arteries, it has a more pronounced effect on smooth muscle vasculature and less effect on myocardial contractility than verapamil. It has no effect on AV conduction and thus has no anti-arrhythmic effects.

**Amlodipine and felodipine**, are more selective than **nifedipine** and have no effect on the myocardial contractility or AV conduction. **Nicardipine** is intermediate in terms of its selectivity. These four agents are used in the treatment of angina and hypertension.

**Isradipine and lacidipine** are virtually specific for their effects on the smooth muscle of peripheral arteries and are only used for the treatment of hypertension.

**Nimodipine** is even more selective in that it acts preferentially on cerebral arteries. Its main use is to prevent vascular spasm following subarachnoid haemorrhage.

#### **Withdrawal of calcium channel blockers**

Sudden withdrawal of calcium channel blockers may precipitate angina or exacerbate angina.

### Ethnic difference in nifedipine kinetics

Sowunmi *et al.* have demonstrated differences in the kinetics of nifedipine for Nigerian, Asian and Caucasian subjects (32). The area under the plasma concentration-time curve (AUC) of nifedipine in Nigerians was significantly higher than for Caucasians after a single 20-mg oral dose. The elimination half life was also longer in Nigerians than Caucasians. No significant differences between Nigerians and South Asians in AUC or half-life of nifedipine were found.

### Drug interactions with calcium channel blockers

<i>Combination</i>	<i>Interaction</i>
<b>Anaesthetics/calcium channel blockers (11)</b>	Verapamil increases the hypotensive effects of general anaesthetics. Risk of AV block.
<b>Anti-arrhythmics amiodarone/calcium channel blockers</b>	There is an increased risk of amiodarone-induced bradycardia and AV block if amiodarone is used in combination with diltiazam or verapamil (11).
flecainide/verapamil (11)	There is an increased risk of myocardial depression and asystole if verapamil is given in combination with flecainide.
quinidine/verapamil (11, 35)	Plasma concentration of quinidine <b>increased</b> by verapamil.
quinidine/nifedipine (11, 36)	Plasma concentration of quinidine <b>reduced</b> by nifedipine.
<b>Antibacterials/calcium channel blockers (11)</b>	Rifampicin increases metabolism of diltiazam, verapamil, and probably nifedipine and other dihydropyridine calcium channel blockers.
<b>Anti-epileptic agents/calcium channel blockers (11)</b>	Diltiazam and nifedipine increase the plasma concentration of phenytoin. The effects of felodipine, isradipine, nicardipine and nifedipine are reduced by carbamazepine, phenobarbitone, phenytoin and primidone. Anticonvulsants, such as carbamazepine, phenytoin and barbiturates, are inducers of cytochrome P450 and cause marked reductions in felodipine plasma levels.

<i>Combination</i>	<i>Interaction</i>
Anti-epileptic agents/ calcium channel blockers Cont.	Patients receiving these drugs will require higher doses of felodipine.
<b>Antihypertensives/ calcium channel blockers (11)</b>	There is potentiation of the hypotensive effect of calcium channel blockers if used in conjunction with any class of antihypertensive therapy including ACE inhibitors.
<b><math>\beta</math>-Adrenergic blockers/calcium channel blockers (11)</b>	$\beta$ -Adrenergic blockers should not be used with either <b>diltiazam</b> (risk of bradycardia and AV block), <b>nifedipine</b> (risk of hypotension and heart failure) or <b>verapamil</b> (risk of a systole, heart failure and severe hypotension). Unlike non-vascular selective calcium channel blockers there is no additive inhibitory effect on cardiac contractility and conduction with felodipine.
<b>Cimetidine/calcium channel blockers (11, 38, 39)</b>	Cimetidine inhibits the metabolism of some calcium channel blockers. Cimetidine is an inhibitor of cytochrome P450 and causes a moderate increase in felodipine plasma concentrations.
<b>Cyclosporin/calcium channel blockers (35, 37–39)</b>	Plasma cyclosporin levels are increased by diltiazam, nicardipine and verapamil
<b>Digoxin/calcium channel blockers (11, 35–39)</b>	Plasma concentrations of digoxin are increased by diltiazam, nicardipine and verapamil with increased risk of AV block and bradycardia. A small increase in digoxin plasma levels has been reported with felodipine tablets but not with the sustained release felodipine formulation.
<b>General anaesthesia/calcium channel blockers (39)</b>	Severe hypotension has been reported during fentanyl anaesthesia with concomitant use of a $\beta$ -adrenergic blocker and calcium channel blockers.
<b>Grapefruit juice/calcium channel blockers (34)</b>	Felodipine, nifedipine, nitrendipine and other dihydropyridine calcium channel blockers plasma levels are moderately increased by grapefruit juice which

<i>Combination</i>	<i>Interaction</i>
	contains high levels of flavonoids which inhibit cytochrome P450.
<b>Lithium/calcium channel blockers (11)</b>	Neurotoxicity may occur without increased plasma lithium levels in patients also receiving verapamil or diltiazem.
<b>Skeletal muscle relaxants/calcium channel blockers</b> tubocurarine/ verapamil, nifedipine (11, 35)	The neuromuscular blocking effect of non-depolarizing muscle relaxants such as tubocurarine are potentiated by verapamil and nifedipine, and possibly other calcium channel blockers.
dantrolene/verapamil (11)	Intravenous dantrolene given to patients on verapamil has led to hypotension, myocardial depression and hyperkalaemia.
<b>Theophylline/calcium channel blockers (38)</b>	Diltiazem caused increases in theophylline blood levels.

#### **4. ADRENERGIC NEURONE BLOCKING DRUGS**

**Guanethidine monosulphate**  
**Bethanidine**  
**Debrisoquine**

These drugs prevent the release of noradrenaline from post-ganglionic adrenergic neurones. Guanethidine also depletes the nerve endings of noradrenaline. These drugs do not control supine blood pressure, and may cause severe postural hypotension. For this reason this subgroup of antihypertensive agents is generally regarded as obsolete. There may be a residual use for them in resistant hypertension, and their role in special cases may be a useful one. Guanethidine monosulphate has found a new therapeutic role in the treatment of glaucoma in an eye drop formulation.

<i>Combination</i>	<i>Interaction</i>
<b>Adrenergic blocker/other drugs with hypotensive action</b> e.g. alcohol (40) antihypertensives (41) diuretics (42, 43) peripheral vasodilators (41) phenothiazines (43) procainamide (44) quinidine (45, 46)	These drugs augment the hypertensive effects of bretylium and guanethidine. Indeed, any drug which lowers blood pressure, either as a primary or secondary pharmacological effect, may augment the action of an antihypertensive drug. The method of interaction differs from one class of antihypertensive drug to another and depends largely upon the way in which the primary antihypertensive drug produces its own effect. In specific instances the interaction may have more than one mechanism which can complicate the ultimate effect, thus, for example, the phenothiazines are reported to potentiate the hypotensive effects of guanethidine and are also found to antagonize the effects of guanethidine by interfering with its uptake into adrenergic neurones.
<b>Antidepressant (tricyclic)/debrisoquine (47–53)</b>	The hypotensive effects of debrisoquine are inhibited by concomitant administration of amitriptyline, imipramine, desipramine or protriptyline (47–51). This interaction is thought to occur primarily at the sympathetic neurone terminal; it has been suggested that tricyclic antidepressants inhibit the uptake of adrenergic neurone-blocking drugs (41, 52, 53).
<b>Fenfluramine/debrisoquine (54)</b>	Fenfluramine (Ponderax) antagonizes the hypotensive action of debrisoquine; although it does not appear to antagonise the hypotensive effects of methyldopa or reserpine.
<b>Mazindol/debrisoquine (55)</b>	Mazindol potentiates the pressor action of catecholamines.
<b>Phenylephrine/debrisoquine (56, 57)</b>	Debrisoquine is a monoamine oxidase inhibitor (MAOI), and exaggerated blood pressure responses to oral phenylephrine have been observed in hypertensive subjects taking debrisoquine (56). This interaction has been confirmed in clinical pharmacology studies (57). Mydriasis due to phenylephrine is potentiated.
<b>Tyramine-containing foodstuff/debrisoquine (58–60)</b>	Debrisoquine is a MAOI. A hypertensive episode occurred in a patient receiving debrisoquine (Declinax) therapy who was given a deliberate tyramine challenge

*Combination**Interaction*

in the form of 50 g of Gruyère cheese (58). This was surprising since debrisoquine has not been found to inhibit intestinal monoamine oxidase in man (59). The rapidity of the onset of the interaction (i.e. within 5 min of cheese ingestion) made it most unlikely that the patient could have absorbed any tyramine from the small intestine. It has been suggested (60) that tyramine can be absorbed via the oral mucosa and that a cheese with a high tyramine content could cause hypertension even though intestinal monoamine oxidase was not inhibited. It was likely, however, that neuronal monoamine oxidase was inhibited.

**Antidepressants  
(MAOI)/guanethidine  
(42)**

MAOIs may antagonize the effects of guanethidine and bethanidine.

**Antidepressants  
(tricyclics)/  
guanethidine  
(42, 43, 61–68)**

Tricyclic antidepressants may antagonize the effects of guanethidine, bethanidine, debrisoquine and clonidine (68). A hypertensive patient was adequately treated with guanethidine (75 mg/day); because of depression he was treated with amitriptyline (25 mg tid) and 300 mg of guanethidine were then required for adequate control. After 5 days of amitriptyline therapy the effects of guanethidine were again eliminated. The hypotensive effect of guanethidine did not return until 18 days after amitriptyline therapy was discontinued (65). The mechanism was thought to be a tricyclic block of transport of guanethidine into the sympathetic neurone.

**Antidiabetic agent/  
guanethidine**  
e.g. insulin  
sulphonylureas  
(chlorpropamide,  
tolbutamide)  
biguanides  
(metformin)  
(69, 70)

Guanethidine therapy has been associated with a reduction in insulin requirements in diabetics. A highly significant improvement in oral glucose tolerance tests was noted during guanethidine administration in three patients with maturity onset diabetes.

<i>Combination</i>	<i>Interaction</i>
<b>Drugs interfering with its uptake into adrenergic neurones/ guanethidine</b> e.g. amphetamines (43, 64, 66, 67, 71) diethylpropion (71) ephedrine (64, 67, 71) mephentermine (71) methylphenidate (66, 71) tricyclic antidepressants (43, 64, 66, 67)	These drugs antagonize the hypotensive action of guanethidine by interfering with its uptake into adrenergic neurones. Larger doses of guanethidine may be required to produce a hypotensive action. When one of these agents is withdrawn in an otherwise stabilized patient a marked hypotensive episode may occur.
<b>Oral contraceptive/guanethidine (72)</b>	The antihypertensive effect of guanethidine is reduced. To treat the hypertension adequately, oral contraceptives may have to be discontinued.
<b>Phenothiazine tranquiliser/guanethidine (41, 43, 67)</b>	Reports conflict as to the nature of this interaction. On the one hand it has been suggested that phenothiazines inhibit the uptake of guanethidine into the adrenergic neurone and thus antagonize its antihypertensive action; this opinion is based upon a preliminary report of a chlorpromazine-guanethidine interaction in one patient (41) and a further report of an adrenergic neurone blocking drug-chlorpromazine interaction, again in one patient (67). On the other hand the phenothiazines are reported to potentiate the effects of guanethidine and other hypotensive drugs (43).
<b>Sympathomimetic amine/guanethidine</b> e.g. amphetamines (43, 64, 66, 67, 71) ephedrine (64, 67, 71)	In guanethidine-treated patients the adrenergic receptor is excessively sensitive to directly acting sympathomimetic amines and there is an increased tendency for cardiac arrhythmias. The increased pressor effect of noradrenaline and phenylephrine in the presence of guanethidine is well documented. A

<i>Combination</i>	<i>Interaction</i>
noradrenaline (67, 73, 74)	marked increase in the pupillary response to phenylephrine eye-drops has been seen in guanethidine-treated patients. Amphetamines and ephedrine antagonize the hypotensive effects of guanethidine.
phenylephrine (67, 75, 76)	
phenylpropanolamine (67)	

## 5. CENTRALLY ACTING ANTIHYPERTENSIVE AGENTS

### a Clonidine hydrochloride

Clonidine hydrochloride is an anti-hypertensive agent with both central and peripheral sites of action. This dual action sets it apart from other adrenergic neurone blocking agents. With long-term treatment clonidine reduces the responsiveness of peripheral vessels to vasoconstrictor and vasodilator substances and to sympathetic nerve stimulation. Early in treatment blood pressure reduction is associated with a central reduction of sympathetic outflow and increased vagal tone.

Clinically there may be bradycardia, reduced venous return and reduced cardiac output. Initially there is no reduction of peripheral resistance, but this tends to fall as treatment continues.

Sudden withdrawal of clonidine may result in rebound hypertension. Termination of treatment should therefore be gradual. If an hypertensive episode does ensue then it should be treated with clonidine or an  $\alpha$ -adrenergic blocking agent such as phentolamine. If clonidine is given concurrently with a  $\beta$ -adrenergic blocking agent then clonidine should not be discontinued until several days *after* the withdrawal of the  $\beta$ -adrenergic blocker (79).

<i>Combination</i>	<i>Interaction</i>
Antidepressants (tricyclics)/clonidine (68, 77-79)	Tricyclic antidepressants antagonize the antihypertensive effect of clonidine. Introduction of desipramine to clonidine treatment in a controlled study led to loss of blood pressure control in four out of five hypertensive patients (68). Previous studies in animals showed the hypotensive action of clonidine was reduced about 20-fold by pretreatment with desipramine (77). An earlier clinical report in one patient stated that the action of clonidine was impaired by the introduction of imipramine (78). The mechanisms involved in this interaction are due to tricyclics impairing the hypotensive action of clonidine by an action inhibiting uptake of the clonidine;

<i>Combination</i>	<i>Interaction</i>
<b>Antidepressants (tricyclics)/clonidine <i>cont.</i></b>	possibly a central effect due to the $\alpha$ -adrenergic blocking action of the tricyclics may also be involved.
<b><math>\alpha</math>-Adrenergic blocking agents/clonidine (79)</b>	$\alpha$ -Adrenergic blocking agents antagonize the acute centrally mediated hypotensive action of clonidine.
<b><math>\beta</math>-Adrenergic blocking agents/clonidine (79)</b>	$\beta$ -Blockers increase the risk of rebound hypertension on clonidine withdrawal. If clonidine and a $\beta$ -adrenergic blocker are given concurrently to control hypertension, clonidine should not be withdrawn until several days after the withdrawal of the $\beta$ -adrenergic blocker.

### b. Methyldopa

Methyldopa exerts a hypotensive effect by interfering with the synthesis and action of noradrenaline. It inhibits the conversion of dopa to dopamine by competing for the enzyme dopa decarboxylase and thus reduces the amount of noradrenaline formed from dopamine. It has also been suggested that the metabolite,  $\alpha$ -methylnoradrenaline, which is much less active than noradrenaline, displaces noradrenaline from its storage sites and acts as a false transmitter.

Methyldopa may induce a positive direct Coombs test in up to 20% of patients treated. This may affect cross-matching for blood transfusion purposes.

Methyldopa may induce haemolytic anaemia. Other side effects are sedation, depression, fluid retention, lupus erythematosus-like syndrome, parkinsonism, diarrhoea, rashes of various forms.

Methyldopa is contra-indicated in patients with phaeochromocytoma, Parkinson's disease porphyria, active liver disease, history of depression.

<i>Combination</i>	<i>Interaction</i>
<b>Antidepressant (MAOIs and tricyclic)/methyldopa (80, 81)</b>	The hypotensive effects of methyldopa may be diminished by MAOI and tricyclic antidepressants; hypertension and central excitation may result from this interaction.
<b>Anti-inflammatory agents (NSAIDS)/methyldopa (11)</b>	NSAIDs antagonize hypotensive reaction of methyldopa

<i>Combination</i>	<i>Interaction</i>
<b>Calcium channel blockers/methyldopa (81)</b>	Increased hypotensive effect.
<b>Carbenoxolone/methyldopa (11)</b>	Carbenoxolone antagonizes hypotensive action of methyldopa.
<b>Corticosteroids/methyldopa (11)</b>	Corticosteroids antagonize the hypotensive action of methyldopa.
<b>Levodopa/methyldopa (82–85)</b>	The interaction between methyldopa and levodopa has been studied in 18 patients with parkinsonism. Together the drugs produced a fall in blood pressure in doses which, when given alone, had no effect or only a slight hypotensive effect. Severe hypotension never occurred. The underlying mechanism of the interaction was thought to be potentiation rather than synergism. Parkinsonism was unaffected by the administration of methyldopa during this short-term study, although there are reports (83–85) of parkinsonism being induced or worsened by methyldopa.
<b>Lithium/methyldopa (11, 81, 86, 87)</b>	A patient on lithium carbonate developed signs of lithium intoxication when methyldopa was introduced into a previously stable state for the control of hypertension. Methyldopa is thought to reduce the rate of renal excretion of lithium. There is a further report of methyldopa increasing the risk of CNS toxicity (87). Increased CNS toxicity with lithium/methyldopa combinations can occur without increased plasma lithium levels (11).
<b>Mazindol/methyldopa</b>	Mazindol potentiates the pressor action of catecholamines: hypertensive response.
<b>Oestrogens/methyldopa (11)</b>	Hypotensive action of methyldopa is antagonized by oral contraceptive agents.
<b>Nitrates/methyldopa (11)</b>	Enhanced hypotensive effect.

<i>Combination</i>	<i>Interaction</i>
<b>Phenothiazines and other antipsychotic agents/methyldopa</b> (11, 81)	Increased risk of extrapyramidal effects. The antihypertensive effect of methyldopa may be antagonized by phenothiazines.
<b>Phenylpropanolamine/methyldopa with oxprenolol</b> (90)	A severe hypertensive episode has been recorded when phenylpropanolamine in a proprietary cold remedy was given to a patient receiving antihypertensive treatment with methyldopa and oxprenolol. (Methyldopa + $\beta$ -adrenergic blocking drugs may produce hypertensive episodes when given together but there was no evidence of this interaction occurring in this patient prior to phenylpropanolamine.)
<b>Propranolol/methyldopa</b> (74, 88, 89)	The combination of methyldopa and intravenous propranolol has been reported occasionally to produce severe hypertension (88). Methyldopa is known to increase the pressor effects of sympathomimetic amines (74), and it has been postulated that $\beta$ -blockade may have a similar action by allowing an unopposed $\alpha$ -constrictor response to adrenergic stimulation (89).
<b>Sympathomimetic amine/methyldopa</b> (11, 74)	The hypotensive effects of methyldopa may be diminished by amphetamine and other sympathomimetic drugs. Methyldopa is also known to increase the pressor effects of sympathomimetic amines.

 **$\alpha$ -Adrenergic blocking agents**

**Doxazosin**  
**Indoramin**  
**Phenoxybenzamine hydrochloride**  
**Phentolamine**  
**Prazosin hydrochloride**  
**Terazosin**

Prazosin has a post-synaptic  $\alpha$ -blocking localised vascular smooth muscle action and consequent vasodilator properties, it rarely causes tachycardia. Prazosin may cause a precipitous reduction in blood pressure after the first dose. Treatment should be initiated with caution at a low dose and increased gradually. Doxazosin and terazosin

have similar properties. Phenoxybenzamine and indoramin also act selectively and competitively on post-synaptic  $\alpha_1$  receptors. Phenoxybenzamine is used with a  $\beta$ -blocker in the acute management of severe hypertensive episodes such as those associated with phaeochromocytoma or in drug-induced hypertensive crises. Phentolamine's use is confined exclusively to the treatment of drug-induced hypertensive crises.

A few cases of extrapyramidal disorders have been reported with indoramin (91). Caution in prescribing to patients with Parkinson's disease is recommended.

<i>Combination</i>	<i>Interaction</i>
<b>Antihypertensive agents/prazosin (91)</b>	Potentiation of the hypotension action of $\alpha$ -adrenergic blocking drugs is achieved by the combination with any other hypotensive agent. Potentiation is most marked with $\beta$ -adrenergic blocking agents.
<b>Chlorpromazine plus amitriptyline/prazosin (92)</b>	A patient who was taking chlorpromazine and amitriptyline showed acute agitation on taking prazosin. The symptoms settled rapidly when prazosin was stopped.
<b>Glyceryl trinitrate/prazosin (93)</b>	The hypotensive effect of prazosin was prolonged when glyceryl trinitrate was given concurrently.
<b>Indomethacin/prazosin (94)</b>	Prazosin-induced hypotension was reduced by indomethacin in four of nine subjects.

#### Tyrosine hydroxylase inhibitors

**Metirosine** inhibits the enzyme tyrosine hydroxylase and hence the synthesis of catecholamines. It is used in the pre-operative treatment of phaeochromocytoma, it is also used long term in patients with phaeochromocytoma who are unsuitable for surgery. In such patients it should be used in conjunction with an  $\alpha$ -adrenergic blocking drug such as phenoxybenzamine. (95)

Metirosine is *not suitable* for the treatment of essential hypertension.

The most common adverse reaction with metirosine is severe sedation. Sedation is maximal after 2–3 days treatment and then tends to diminish and is not a problem after 7–10 days. Patients should be warned about the risk of sedation and advised not to drive or operate machinery. *Metirosine sedation is enhanced by alcohol and other CNS depressants, e.g. hypnotics sedatives, tranquillisers and anxiolytics.*

Extrapyramidal signs such as drooling, speech difficulties and tremor occur in about 10% of patients. The extrapyramidal side effects of phenothiazines and haloperidol are potentiated. Diarrhoea, breast swelling and galactorrhoea have also been reported, as have nasal stuffiness, headache, impotence and ejaculation failure.

### Ganglion-blocking agents

**Trimetaphan camsylate** is a short acting ganglion-blocking agent which also has a direct vasodilator effect on peripheral vessels. It has a rapid short and reversible action which permits minute-to-minute control of blood pressure. Trimetaphan is therefore used to induce controlled *hypotension* during surgical procedures, e.g. neurosurgery, vascular surgery, prostatectomy, thyroidectomy, etc. (96).

Trimetaphan may sensitise the patient to the cardiovascular effects of both endogenous and exogenous sympathomimetic amines.

Ganglion blockade due to trimetaphan may reduce gastrointestinal mobility, cause urinary retention, impair visual accommodation, raise intraocular pressure and may, on occasion, induce hypoglycaemia and hypokalaemia.

Ganglion blockers as a group were first line treatment for control of hypertension in the 1960s, but agents such as hexamethonium bromide, mecamylamine hydrochloride, pempidine tartrate, and pentolinium tartrate are now generally regarded as obsolete.

<i>Combination</i>	<i>Interaction</i>
<b>Skeletal muscle relaxants/trimetaphan (96))</b>	Care should be taken using trimetaphan with suxamethonium.
<b>Sympathomimetic amines/trimetaphan (96))</b>	Trimetaphan may sensitise the patient to the cardiovascular effects of sympathomimetic amines.

### Vasodilator antihypertensive drugs

This group consists of potent drugs, especially so when used in conjunction with a  $\beta$ -adrenergic blocking agent and a diuretic. These agents should be used to control hypertensive crises or malignant hypertension resistant to other treatment.

**Diazoxide** administered by mouth is useful in the management of patients with chronic hypoglycaemia from excess endogenous insulin secretion, either from an islet cell tumour or islet cell hyperplasia. Retention of sodium and water are common. Extrapiramidal side effects, cardiomegaly, leucopenia and thrombocytopenia have occurred. Diazoxide is also given by rapid intravenous injection for the control of severe renal hypertension. Side effects include tachycardia, hyperglycaemia, and sodium and water retention. Other adverse reactions that have been reported are hyperosmolar non-ketotic coma, cardiomegaly, leucopenia, thrombocytopenia and hirsutism.

### Drug interactions with diazoxide

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulants/diazoxide</b> (97)	Anticoagulation potentiated.
<b>Diuretics/diazoxide</b> (97)	Diuretic effects potentiated.
<b>Antihypertensive agents/diazoxide</b> (97)	Hypotensive effects potentiated.

**Hydralazine** is a direct vasodilator which exerts its principal effect on the arterioles. Its precise mode of action is unknown. In clinical use to control severe or resistant hypertension it produces a fall in peripheral resistance and a decrease in arterial blood pressure, which in turn induces reflex compensatory responses via the sympathetic system and by salt and fluid retention with oedema and reduced urinary volume. It is therefore generally used in combination with a  $\beta$ -adrenergic blocking agent and a diuretic to reduce these compensatory reflex responses.

The 'overall' hyperdynamic state of the cardiovascular system in its reflex responses to the profound vasodilation may by myocardial stimulation provoke or aggravate angina. Patients with coronary artery disease should therefore only be given hydralazine with a  $\beta$ -adrenergic blocker. Long-term treatment with hydralazine may provoke a lupus erythematosus-like syndrome, the first symptoms of which are likely to be arthralgia, fever, and rash. In its more severe form it resembles acute SLE, and renal and ocular involvement may occur. Long-term treatment with corticosteroids may be necessary to control these LE like effects. Slow acetylators and women are most likely to develop LE syndrome.

Rare side effects include blood dyscrasias; abnormal liver function tests, jaundice and hepatitis; proteinuria; arthralgia and myalgia, paralytic ileus (97).

### Drug interactions with hydralazine

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/hydralazine</b> (11, 18)	Enhanced hypotensive effect.
<b>Aldesleukin/ hydralazine</b> (11)	Enhanced hypotensive effect.

<b>Anaesthetics/ hydralazine (11)</b>	Enhanced hypotensive effect.
<b>Antidepressants/ hydralazine (11, 98)</b>	Tricyclic antidepressants and major tranquillisers enhance the hypotensive effect. Caution should be particularly exerted with concurrent use of MAOIs.
<b>Antihypertensive agents/hydralazine (11, 98)</b>	ACE inhibitors, $\beta$ -adrenergic blockers, calcium antagonists and diuretics all potentiate the hypotensive effect of hydralazine.
<b>Corticosteroids/ hydralazine (11)</b>	Corticosteroids antagonize the hypotensive effect of hydralazine.
<b>Levodopa/hydralazine</b>	Levodopa potentiates hydralazine.
<b>Muscle relaxants/ hydralazine (11)</b>	Baclofen potentiates the hypotensive effects.
<b>NSAIDs/hydralazine (11)</b>	NSAIDs antagonize the hypotensive action of hydralazine.
<b>Sex hormones/ hydralazine (11)</b>	Oestrogens (HRT) and combined oral contraceptive preparations antagonize the hypotensive effect of hydralazine.

**Sodium nitroprusside** is given by intravenous infusion to control severe hypertensive crises. The action is directly on vascular musculature and is achieved independently of the autonomic nervous system. Duration of effect is brief due to the rapid conversion to cyanide and then thiocyanate. This permits minute by minute control of the haemodynamic effects.

The precautions as to the use of sodium nitroprusside are similar to those of hydralazine, with the additional precaution of use in patients with hypothyroidism because thiocyanate inhibits both the re-uptake and binding of iodine by the thyroid.

If overd dosage occurs, the symptoms being that of cyanide poisoning, stop the nitroprusside infusion. Thiosulphate or dicobalt edetate, or hydroxycobalamin should be administered as an antidote; ancillary oxygen therapy should also be given.

Drug interactions for sodium nitroprusside: interactions are as for hydralazine.

**Minoxidil** exerts its hypotensive action by action on the smooth muscle vasculature. Minoxidil is contraindicated in patients with phaeochromocytoma. Like diazoxide and hydralazine it is normally given with a diuretic and  $\beta$ -adrenergic blocker since

vasodilation is accompanied by reflex cardiac output and fluid retention. Soon after starting minoxidil, 60% of patients exhibit ECG changes, these changes disappear with continuing treatment. Pericardial effusions have been detected in some patients, but a cause and effect relationship has not been established. Minoxidil has also been found to stimulate hair growth and is used topically for this purpose.

Drug interactions for minoxidil: interactions are as for hydralazine.

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## **2.3. DRUG INTERACTIONS WITH ANTICOAGULANTS AND FIBRINOLYTIC AGENTS**

### **1. ORAL ANTICOAGULANTS (INDIRECT ANTICOAGULANTS)**

#### **i. Coumarin Derivatives**

**Dicoumarol** (Dicoumarin, Bishydroxycoumarol USP)

**Ethyl biscoumacetate**

**Nicoumalone**

**Phenprocoumon**

**Warfarin sodium**

#### **ii. Indandione Derivatives**

**Anisindione**

**Diphenadione**

**Phenindione**

The coumarins and indandiones are synthetic compounds which are effective after oral dosage. Unlike heparin they have no effect on clotting if added to whole blood *in vitro*. They act indirectly, that is they must be absorbed and metabolized by the body before they produce an effect. It is known that they interfere with the hepatic formation of prothrombin and at least three other factors concerned in blood clotting. The anticoagulant action of both these groups of drugs is similar; they differ only in the intensity and duration of action of a given dose. With all these agents, there is a delay of at least 12 hr before any effect is observed; this delay is not due to slow absorption but is a reflection of the necessity for this type of drug to be metabolized before it exerts its effect. These indirect anticoagulants can be antagonized by phytomenadione (vitamin K<sub>1</sub>) which can be given orally, intramuscularly or intravenously.

Contraindications for use of the oral anticoagulants are as for the use of heparin; apart from haemorrhage other toxic effects are uncommon. The coumarins occasionally cause skin rashes and alopecia but have not been responsible for any major toxic effects other than areas of tissue necrosis; although rare, cases have been reported in France, Germany, The Netherlands, Sweden, Switzerland, USA and the United Kingdom (these areas of necrosis affect buttocks, breasts, thighs and in

most cases have appeared within a few days of commencing therapy and most cases have appeared in obese women). The problem of anticoagulant skin necrosis has been reviewed by Jones and Staffa (1) and by Griffin (2). On the other hand, phenindione has been occasionally incriminated in serious and occasionally fatal toxic reactions, particularly exfoliative dermatitis, hepatic and renal damage, and blood dyscrasias.

### **SUMMARY: ONSET AND DURATION OF ACTIVITY OF THE ORAL ANTICOAGULANTS**

#### **Short-acting**

**Ethyl biscoumacetate** Stable anticoagulation is hard to achieve even if the drug is given 6-hourly and the prothrombin time must be estimated every other day while it is being given. Maximum therapeutic effect occurs within 18–30 hr; the prothrombin time usually returns to normal within 48 hr of administration of the last dose.

#### **Intermediate-acting**

**Phenindione** Phenindione was popular until it became known that it can cause serious and occasionally fatal toxic reactions. A therapeutic effect is evident within 24–30 hr, and full effect within 36–48 hr. The anticoagulant effect usually ceases within 30 hr of stopping therapy.

**Nicoumalone** Maximum therapeutic effect occurs within 36–48 hr; the prothrombin time usually returns to normal within 48–72 hr of administration of the last dose.

#### **Long-acting**

**Anisindione** Maximum therapeutic effect occurs within 34 hours; prothrombin depression may persist for up to 3 days after cessation of therapy.

**Dicoumarol** The original coumarin anticoagulant, dicoumarol, is now little used; it is absorbed slowly and erratically. Development of therapeutic effect takes from 24 to 72 hr; the effect may persist for 96 hr or more after dosage is stopped.

**Warfarin sodium** This is the most commonly prescribed coumarin derivative; it is equally effective orally or intravenously, and may also be given intramuscularly; development of therapeutic effect takes from 12 to 18 hr and may persist for 5–6 days.

**Phenprocoumon** Maximum therapeutic effect occurs within 24–48 hr; it takes 7–14 days for the prothrombin time to return to normal after the last dose. More

Table 1. LEVEL 1 INTERACTIONS WITH WARFARIN

<i>Therapeutic group</i>	<i>Potentiation</i>	<i>Inhibition</i>
Antibiotics and antimicrobials	co-trimoxazole erythromycin fluconazole isoniazid metronidazole miconazole	griseofulvin naftillin rifampicin
Cardiac	amiodarone clofibrate propafenone propranolol sulphapyrazone	cholestyramine
Anti-inflammatory	phenylbutazone piroxicam	—
CNS	alcohol	barbiturates carbamazepine chlordiazepoxide
Gastro intestinal	cimetidine omeprazole	sucralfate
Miscellaneous	—	high vitamin K content foods, large amounts of avocado

than one dose of vitamin K<sub>1</sub> may be needed if reversal of effect is required during treatment.

### Very long-acting

**Diphenadione** Maximum therapeutic effect occurs within 48–72 hr; prothrombin depression may persist for as long as 20 days after dosage ceases.

In a detailed literature review of reported warfarin interactions citations, 793 were retrieved and examined by Wells *et al.* (3) who scored the level of probability of such drug interactions with warfarin as:

level 1, highly probable; level 2, probable; level 3, possible; level 4, doubtful that a clinically important interaction had or had not occurred. These assessments for level 1 interactions are summarized in Table 1.

## 2. INTRAVENOUSLY ADMINISTERED AGENTS

### i. Alteplase (TPA) (Actilyse)

Alteplase is a tissue plasminogen activator (TPA) produced by recombinant technology. Alteplase is a glycoprotein which activates the conversion of plasminogen to plasmin. When administered intravenously alteplase remains inactive in the circu-

lation until it binds to fibrin, for which it has a high affinity. Activation of alteplase by fibrin causes a local conversion of plasminogen to plasmin, thus inducing thrombolysis of the clot. After intravenous injection alteplase is cleared rapidly from the circulation by liver catabolisms, the  $t_{1/2}$  being of the order of 5 min.

Alteplase and anistreplase should not be used in patients: (i) with a history of cerebrovascular disease with uncontrolled hypertension in view of the risk of cerebral haemorrhage; (ii) with known bleeding diathesis; (iii) within 10 days of major trauma or surgery; (iv) with active peptic ulceration; (v) with acute pancreatitis; (vi) with bacterial endocarditis; (vii) with severe liver disease, with or without portal hypertension, with oesophageal varices; (viii) with proliferative diabetic retinopathy.

Alteplase does not cross the placental barrier. Allergic reactions, anaphylaxis and Guillain-Barre syndrome have rarely been reported with these therapies.

Pharmacokinetic interactions with alteplase are largely expected on theoretical grounds to be confined to interactions that alter the hepatic blood flow (HBF) and therefore the hepatic clearance of alteplase (4).

In de Boer and van Griensven's review of this area they point out that

In animal experiments, changes in the pharmacokinetics of alteplase have been demonstrated with compounds that alter HBF. Sodium nitroprusside increased plasma concentrations of alteplase in rabbits and epoprostenol (prostacyclin) produced an increase in CL of alteplase by 30% to 40% in dogs. This corresponded with the numerous human and animal studies in which it was demonstrated that nitrovasodilators decrease and epoprostenol increases HBF.

The routine administration of heparin, aspirin,  $\beta$ -blockers and nitrates concurrently with alteplase is recommended. Furthermore, treatment of chest pain by opioids, of cardiac rhythm disturbances by antiarrhythmics and of cardiogenic forward failure by inotropic agents may be indicated during alteplase administration.

As mentioned above heparin does not influence the pharmacokinetics of alteplase. Similarly, such an interaction is not expected between aspirin and alteplase. Acute administration of nitrates and  $\beta$ -blockers produce a decrease in HBF and calcium antagonists produce an increase. Therefore, these compounds are expected to influence the plasma concentration of alteplase.

Lignocaine, atropine, dopamine and morphine in normal therapeutic doses do not alter hepatic blood flow in man and therefore on theoretical grounds should not cause clinical problems.

## **ii. Ancrod (Venom of Malayan pit-viper) (Arvin)**

Anticoagulation is produced by controlled defibrillation. Ancrod acts enzymically on the fibrin molecule to form a product which cannot be clotted by physiological thrombin. Ancrod cleaves fibrinogen to split off A-fibropeptides (A, AY, AP), but not fibropeptide B, to produce a friable, unstable, urea-soluble, non-cross-linked particulate fibrin particle, 1–2  $\mu\text{m}$  long. This fibrin has degraded  $\alpha$ -chains, is rapidly digested by plasmin and is rapidly removed by phagocytosis in the reticulo-endothelial system or by fibrinolysis. Overdose with ancrod should be treated with the specific antidote of anti-venom serum.

**iii. Anistreplase (Eminase)**

Anistreplase is a streptokinase-plasminogen complex with an anisoyl group reversibly placed within the catalytic centre of the plasminogen moiety (5). In common with streptokinase, anistreplase is inactive on injection, and activation occurs in a controlled fashion by hydrolysis of the anisoyl group directly after its administration. After its activation anistreplase largely behaves similarly to streptokinase. It is metabolized in the liver, its  $t_{1/2}$  is of the order of 60–90 min.

**iv. Epoprostenol**

Epoprostenol is a prostacyclin, it is given to inhibit platelet aggregation during cardiopulmonary bypass and charcoal haemoperfusion, and as an alternative to heparin in renal dialysis. Since its half-life is only about 3 min it must be given by continuous intravenous infusion. It is a potent vasodilator and therefore its side effects include flushing, headache and hypotension.

Epoprostenol should not be administered to pregnant women and there is no information on its effects on lactation since, like other prostaglandins, it has an action on smooth muscle and can induce uterine contractions.

**v. Heparin BP (Heparin Sodium, Soluble Heparin, Sodium Heparin USP)**

Heparin is a sterile preparation containing the sodium salt of a complex organic acid present in mammalian tissues; it is isolated from beef lung or other mammalian sources and has the characteristic property of preventing clotting of blood. It produces its anticoagulant effect by inhibiting the conversion of prothrombin to thrombin and also inhibiting the thrombin conversion of fibrinogen to fibrin. This anticoagulant action can be neutralized by protamine sulphate (Protamine Sulphate Injection BP, Protamine Sulphate for Injection USP).

Heparin is poorly absorbed by mouth; after intravenous or intramuscular injection it is extensively bound to plasma proteins; it is inactivated in the liver and is found in the urine largely as uroheparin, a degraded form of heparin. Heparin does not cross the placenta and does not appear in breast milk (6).

As with other anticoagulants the main danger of therapy with heparin is haemorrhage. Heparin therapy should be instituted with extreme caution in patients with a known pre-existing tendency to bleed, in subacute bacterial endocarditis, gastric or duodenal ulcer, haemophilia, malignant disease, advanced renal or liver disease and pregnancy. Menstruation is not a contraindication to the use of heparin.

If heparin is to be administered by adding it to an intravenous infusion fluid, then care must be given to the choice of infusion fluid otherwise the heparin will be rapidly inactivated.

Prolonged heparin therapy causes osteoporosis and increased urinary calcium loss. Low molecular weight or fractionated heparin in various formulations are available and are usually given once daily by subcutaneous injection for the prevention of venous thromboembolism. They have a longer duration of action than unfractionated heparin.

**vi. Urokinase**

Urokinase is a 2 (ukidan)-chain serine protease which, like streptokinase, lacks fibrin specificity. It directly activates plasminogen without forming a complex. It is subject to hepatic inactivation and has a  $t_{1/2}$  of 15–20 min.

**vii. Saruplase (Pro Urokinase)**

The unglycosylated human single-chain urokinase plasminogen activator is a relatively fibrin-specific thrombolytic agent. A proportion of saruplase is converted to urokinase *in vivo*. The exact mechanism by which saruplase exerts its action is unknown, but some of its activity must be due to its conversion to urokinase.

**viii. Streptokinase (kabikinase, streptase)**

Streptokinase is a single-chain non-fibrin-specific thrombolytic agent. Usually 1.5 million U are given as a continuous intravenous infusion over 1 hr. Following its administration, streptokinase is activated after formation of a complex with circulating plasminogen (7). This complex converts noncomplexed plasminogen to plasmin irrespective of whether it is bound or unbound fibrin (clot). Streptokinase is cleared from plasma largely by the liver. The half-life ( $t_{1/2}$ ) is of the order of 30–60 min.

Rapid infusion of streptokinase can lead to a substantial reduction in blood pressure, probably by excessive activation of the kallikrein–kinin system. Petch (8) has reviewed the dangers of thrombolysis.

Thrombolytic therapy with streptokinase during the first 18 weeks of pregnancy should be avoided, since there is an increase risk of placental separation. Negligible amounts of streptokinase cross the placenta, foetal blood concentrations being less than 1/1000 the maternal blood levels.

### **3. DRUG INTERACTIONS WITH COUMARIN ANTICOAGULANTS**

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulant/alcohol (9, 10)</b>	Acute alcohol intake even in moderate amounts potentiates the action of coumarin anticoagulants by inhibition of their hepatic enzyme metabolism. In alcoholics the half-life of warfarin is reduced due to alcohol-induced stimulation (induction) of liver microsomal enzymes.
<b>Anticoagulant/ allopurinol (11–14)</b>	Allopurinol potentiates the anticoagulant action of warfarin. It is thought that the interaction is due to inhibition of warfarin metabolism (13). Allopurinol has

<i>Combination</i>	<i>Interaction</i>
<b>Coumarin anticoagulant/ amiodarone</b>	been shown to increase the plasma half-life of bishydroxycoumarin.
<b>Anticoagulant/ anabolic steroid (11, 18–21)</b> e.g. drostanolone ethyloestrenol methandienone methandriol methenolone nandrolone norethandrolone oxandrolone oxymesterone oxymetholone stanozolol	Five of nine patients given amiodarone while on established warfarin treatment presented with bleeding phenomena 3–4 weeks later; warfarin dosage required reduction by 30% to re-establish anticoagulant control; these warfarin-potentiating effects persisted up to 4 months after amiodarone was stopped (15). In one patient (16) the addition of amiodarone on two occasions led to dangerous increases in the anticoagulant effects of warfarin in one patient (16). Animal studies (16) and other case reports have confirmed this interaction (17). Its mechanism has not yet been established but it may be due to displacement of warfarin from protein binding sites or, alternatively, to altered warfarin metabolism.
<b>Anticoagulant/ anti-inflammatory analgesic drugs</b> aspirin and other salicylates (9, 18, 20)	A number of patients receiving oral anticoagulants and anabolic steroids have developed haemorrhages. This interaction is thought to be due to reduced clotting factor synthesis. In addition, anabolic steroids are thought to potentiate the anticoagulant action of coumarins by increased receptor site affinity.
	These displace coumarins from plasma protein-binding sites and thereby potentiate their anticoagulant action. Salicylates also tend to reduce plasma prothrombin levels. Aspirin has an ulcerogenic action and also gives rise to occult bleeding from superficial gastric erosions. Haemorrhage is made worse if these drugs are used in combination. Aspirin should be avoided completely by patients on

*Combination**Interaction***Anticoagulant/  
anti-inflammatory  
analgesic drugs *cont.***

oral anticoagulant treatment. There is some evidence to suggest that sodium salicylate is less likely to produce gastrointestinal bleeding; however, all salicylates should be used with caution in such patients.

**azapropazone  
(22, 23)**

This compound, which is structurally related to phenylbutazone, displaces warfarin from plasma-protein binding sites and thus potentiates its anticoagulant action. The mechanism of this interaction may also depend on the effect of azapropazone on the renal clearance of the R and S isomers of warfarin.

**diflunisal (24)**

Addition of diflunisal to warfarin regimes in five normal subjects did not alter clotting tests, but total warfarin concentration in serum decreased from 0.74 to 0.63 µg/ml. Increase in unbound warfarin level (1.024–1.337%) was directly related to plasma diflunisal concentration. Warfarin level took 12 days to return to 0.71 µg/ml when diflunisal was stopped. The clinical significance of this interaction has yet to be established.

**dextropropoxyphene  
and paracetamol (25)**

Two patients developed gross haematuria when Distalgesic was given during the course of warfarin anticoagulant therapy. It is thought that the interaction is due to inhibition of warfarin metabolism by dextropropoxyphene. In one of the above patients the plasma warfarin level increased from 5.9 to 7.8 µmol/l despite reduction in dosage. A reduction in warfarin dosage in anticipation of this reaction is recommended if dextropropoxyphene is given concomitantly.

**flurbiprofen (26)**

Two patients, both stabilized for several years on acenocoumarol (13–41 mg/week), developed haematomas and haematuria or melaena 2–3 days after flurbiprofen (150–300 mg/day). In one case, the Thrombotest time increased from 158 sec before flurbiprofen to 13.5 min after; in the second case the increase was from 127 to 200 sec. Discontinuation of

<i>Combination</i>	<i>Interaction</i>
indomethacin (18, 27–30)	flurbiprofen and acenocoumarol and initiation of i.v. phytomenadione led to recovery within 3.5–6 weeks and both patients resumed acenocoumarol without adverse effects. Avoid this combination.
ketoprofen (31) naproxen (31)	Peptic ulceration, possibly with gastrointestinal haemorrhage, may occur with indomethacin therapy, and could become severe if an anticoagulant drug is given concomitantly. It has also been suggested that indomethacin may displace coumarins from plasma protein binding sites thus resulting in an enhancement of their anticoagulant action (28). Avoid this combination if possible; if drugs have to be given together, use with caution since ulcerogenic action of indomethacin may complicate the interaction. Substitution of ibuprofen for indomethacin in one case re-established anticoagulant control (30).
mefenamic acid (18, 20, 31)	These two drugs for the treatment of various forms of arthropathy are rapidly absorbed after oral administration. They become bound to plasma protein and may displace other drugs that compete for the same binding sites, thereby increasing their activity, and particular care is necessary with anticoagulants. Neither drug seems to induce microsomal enzymes in the liver.
paracetamol (acetaminophen) (9, 33–36)	It has been reported that mefenamic acid may enhance the effects of coumarin anticoagulants (32), possibly by displacement from plasma protein binding sites (31). Although said to be less likely to produce gastrointestinal haemorrhage than aspirin, its use in conjunction with anticoagulants requires caution.
	Reports on a paracetamol–coumarin interaction are controversial; indeed there are doubts as to whether such an interaction occurs (9, 33) or, if it does, whether it is of clinical significance (34). However, paracetamol has been tabulated among drugs which are capable of potentiating oral anticoagulants, although such entry is qualified by relating it to high dosage for several weeks (35). Interest has been raised

*Combination**Interaction***Anticoagulant/  
anti-inflammatory  
analgesic drugs *cont.***

again by a new report on 20 patients which indicates that such interaction does occur and that it is of sufficient clinical importance to require reduction in anticoagulant dosage in some patients. It was suggested that the interaction might be related to interference with hepatic synthesis of factors II, VII, IX and X (36).

phenylbutazone  
(9, 18, 20, 37)  
oxyphenbutazone  
(18, 20)

These related drugs both displace coumarins from plasma protein binding sites and thus potentiate their anticoagulant effects. Also like other anti-inflammatory (antirheumatic) agents they are ulcerogenic and in such combination there may be bleeding from drug-induced gastrointestinal lesions and ulcers.

piroxicam (38)

A 60-year-old man was taking warfarin 20 mg weekly, piroxicam 20 mg daily and flurazepam 15 mg noct. as required with a stable prothrombin time in the therapeutic range. Stopping the piroxicam resulted in a decreased prothrombin time. Two further rechallenges over 10 months supported the impression that piroxicam potentiates the hypoprothrombinaemic response to warfarin. Piroxicam is an enolic derivative structurally similar to phenylbutazone. By analogy the piroxicam interaction with warfarin may be due to changes in protein binding, and an effect on metabolism which may be stereoselective for the S isomer of warfarin.  
The addition of piroxicam may be expected to increase the prothrombin time of patients maintained on warfarin.

sulindac (39, 40)

Two reports involving three patients suggest that sulindac potentiates the anticoagulant effects of warfarin. A report on 19 normal subjects suggests that it does not (41).

Anticoagulant/antacid  
(42)

There is some evidence to suggest that concomitant administration of antacids may cause impaired absorption of coumarin anticoagulants. The alkaline environment produced by them causes a larger

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulant/ antibiotic or antibacterial agent</b> cephaloridine (11, 43)	proportion of ionized anticoagulant which is not so well absorbed as the un-ionized form.
chloramphenicol (18)	Produces prolonged prothrombin times and potentiates the anticoagulant effect due to impaired vitamin K absorption from gut.
co-trimoxazole and other sulphonamide + trimethoprim combinations	Chloramphenicol potentiates the action of anticoagulants by two mechanisms: (i) impairment of absorption of vitamin K from the gut and (ii) inhibition of coumarin metabolism in the liver.
erythromycin (45)	Potentiation of the anticoagulant action of warfarin has been described by a number of workers. The mechanism of action is uncertain but could be due to decreased synthesis of vitamin K due to action of co-trimoxazole on the gut flora, or due to displacement of warfarin from plasma binding sites or, as has been suggested, due to inhibition of warfarin metabolism. The interaction appears to be stereoselective with the S isomer of warfarin (44). A reduction in warfarin requirements should be anticipated if co-trimoxazole is given to a patient stabilised on warfarin. It is nearly always preferable to give trimethoprim alone rather than co-trimoxazole or other sulphonamide/trimethoprim combinations.
fluconazole	Potentiation of anticoagulant effect of warfarin.
	A recent report has described a warfarin-stabilized patient in whom there was a prolonged prothrombin time associated with nose bleeds, bleeding gums and melaena when fluconazole was given (46). Similar cases and studies of potential potentiation of the anticoagulant action of warfarin by fluconazole have been reported (47-50). Fluconazole has also been reported to potentiate warfarin, phenytoin and tolbutamide (51).

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulant/ antibiotic or antibacterial agent cont.</b>	Griseofulvin causes an increased rate of coumarin metabolism due to enzyme induction; this antagonizes the anticoagulant effect.
griseofulvin (9, 18, 20, 52)	
kanamycin (53)	Kanamycin may decrease vitamin K synthesis by intestinal bacteria and, if administered for more than a few days may, by this mechanism, potentiate the effects of oral anticoagulants.
latamoxef sodium (54–56)	Marked prolongation of bleeding time with haemorrhage has been recognized in patients receiving latamoxef sodium; this coagulopathy is reversible with vitamin K (54–56). The mechanism of this reaction has been suggested as platelet inhibition mediated by antibiotic binding to the platelet surface; the time schedule in some patients was too short for suppression of vitamin K-producing gut microflora to be responsible for the coagulopathy. A review article (56) has cited 29 cases of hypoprothrombinaemia caused by latamoxef and occasional bleeding in debilitated patients.
metronidazole (57)	Oral metronidazole is being increasingly used in the treatment of anaerobic infections and also as a prophylactic measure against anaerobic infections in patients undergoing surgery in addition to its original use as a trichomonicidal agent. Metronidazole inhibits warfarin metabolism due to its disulfiram-like action inhibiting aldehyde dehydrogenase and hydroxylating enzyme systems. Warfarin exists as two optical isomers S(–) warfarin which is metabolized to 7-hydroxy-warfarin and R(+) warfarin which is metabolized to 6-hydroxy-warfarin and then to warfarin alcohols. The effect of metronidazole seems to be stereospecific for S(–) warfarin. If introducing metronidazole to a stabilized anticoagulated patient, reduce warfarin dosage in anticipation of interaction.
nalidixic acid (20, 31)	This urinary antiseptic is bound in high proportion to plasma proteins; it displaces warfarin sodium from

<i>Combination</i>	<i>Interaction</i>
neomycin sulphate (9, 18)	plasma binding sites in <i>in vitro</i> studies and thus may potentiate the effect of the anticoagulant.
streptomycin sulphate (58)	These drugs reduce the amount of vitamin K synthesized by intestinal bacteria and this may potentiate the effect of an oral anticoagulant.
sulphonamides (11, 18)	Sulphonamides also displace coumarins from protein binding sites and so potentiate their anticoagulant effect.
tetracyclines (11, 18, 59)	In one patient sulphafurazole, like all 'sulfa' drugs, displaced warfarin from protein binding sites within 48 hr of start of concomitant dosage and potentiated anticoagulant effects causing gross haematuria (60).
tetracyclines	A patient on warfarin (5 and 7.5 mg orally on alternate days) to maintain patency of a femoral-popliteal bypass graft showed enhanced anticoagulation after starting on tetracycline (250 mg orally qds) for the treatment of chronic blepharitis. His INR fell from 2.0–3.0 to 2.7. Over the next several months, changes in INR generally paralleled changes in the tetracycline dosage (61).
<b>Anticoagulant/ anticonvulsants</b> carbamazepine felbamate phenobarbitone phenytoin (diphenylhydantoin) (20, 62–64)	When anti-epileptic drugs are taken in a steady-state situation they do not result in unstable anticoagulant control; such drugs are, however, potentially capable of interacting to reduce coumarin half-life by their enzyme-inducing action.
	Carbamazepine induces microsomal enzymes and shortens the plasma half-life of warfarin, lowers serum warfarin concentrations, and reduces the hypothrombinaemic effect under controlled conditions.
	Discontinuing carbamazepine in one patient resulted in a potentially dangerous increase in prothrombin time.

*Combination**Interaction***Anticoagulant/  
anticonvulsants cont.**

Care should be taken to adjust warfarin dosage when stopping or starting carbamazepine in a patient stabilized on anticoagulants.

A male patient with a long-standing aortic valve replacement was receiving a weekly warfarin dose of 35 mg to maintain a target INR of 2.5 to 3.5. Monotherapy for seizures with felbamate (2400 mg/day) was started and raised to 3400 mg/day after 2 weeks. Two weeks after felbamate was started his INR had increased to 7.5. Warfarin was therefore withheld for 3 days and restarted at a dose of 5 mg/day. Three weeks later the INR had risen to 18.2 and warfarin was withheld again for 4 days and restarted at a dose of 2.5 mg/day. The INR then stabilized within the target range. At no stage did the patient experience signs of bleeding. It was thought that felbamate had inhibited warfarin's metabolism (65).

Phenytoin may displace coumarins from plasma-binding sites and therefore potentiate their anticoagulant effect. Inhibition of coumarin metabolism increases their plasma half-life from 9 to 36 hr (20).

Dicoumarol inhibits the metabolism of phenytoin in the liver and thus potentiates its anticonvulsant effect (66); other coumarins may be expected to have this action, but not phenindione.

**Anticoagulant/  
antidepressant MAOIs  
(11, 67, 68)**

e.g.

- phenelzine
- iproniazid
- isocarboxazid
- mebanazine
- nialamide
- phenoxypropazine

MAOIs potentiate the anticoagulant action of coumarins and may cause severe haemorrhage.

<i>Combination</i>	<i>Interaction</i>
<b>Tricyclic compounds</b> (11, 69, 70) e.g. amitriptyline desipramine dibenzepin imipramine	Tricyclic antidepressants enhance the anticoagulant effect of coumarin drugs due to their inhibition of the liver metabolism of the anticoagulants. This may result in haemorrhage.
<b>Anticoagulant/ antidiabetic agent</b> chlorpropamide (71) glibenclamide (73) tolbutamide (18, 72)	Interactions are complex and mutual. The sulphonylureas and coumarin anticoagulants compete for plasma protein binding sites. The sulphonylureas displace coumarins increasing their anticoagulant action; this is followed by an antagonism of anticoagulant effect due to increased metabolism of the coumarins. Dicoumarol (bishydroxycoumarin) increases the half-life of tolbutamide in diabetics and in normal subjects (72). A similar effect has been described with chlorpropamide (71). The elevated blood levels of tolbutamide may precipitate hypoglycaemia and may also increase the displacement of dicoumarol from plasma binding sites.
<b>Anticoagulant/ antimalarial agent</b> proguanil (74-76)	A 77-year-old woman was maintained on warfarin for over 30 years without difficulty. Forty-eight hours after starting glibenclamide, she experienced bruising around her right shoulder and upper arm, spreading to the soft tissue of her chest wall and tracking down towards her abdomen. Her INR had increased from 2.3 to 6.6. She was given fresh frozen plasma and warfarin was stopped. Despite further transfusions with fresh frozen plasma and fresh packed cells her coagulation remained abnormal (INR 5.2). Glibenclamide was stopped and within 24 hr her INR had returned to normal (INR 2.2). However, her soft tissue haemorrhage extended and formed two large haematomas which became infected. The patient died (73).

A 59-year-old woman stabilized on warfarin for 9 years, presented with a 4-day history of haematuria, bruising, abdominal and flank discomfort, and nausea and vomiting. She had also been taking proguanil as a

*Combination**Interaction***Anticoagulant/  
antimalarial agent cont.**

prophylactic agent for 6 weeks. All drugs were stopped and she was admitted to hospital. She had a high prothrombin ratio (8.6) and other abnormal blood values. She was treated with plasma and vitamin K and her haematuria ceased after 3 days, and she remained well thereafter with no other bleeding (74).

There are no previous reports of such an interaction. However, proguanil is a prodrug that is metabolized to cycloguanil which is structurally related to trimethoprim, which has been reported to enhance the effects of warfarin (75, 76). The mechanism of the interaction is not known but it is unlikely to involve changes in albumin binding of warfarin since only 14% of circulating proguanil is in the bound form (76). It has been suggested that antimalarial prophylaxis should not include proguanil in patients taking warfarin (74).

**Anticoagulant/  
antithyroid agent**  
thiouracil  
methylthiouracil  
propylthiouracil

The thiouracils may produce hypoprothrombinaemia; the mechanism for this is unknown (77, 78)

**Anticoagulant/  
antituberculous agents**  
rifampicin (Rifadin,  
Rimactane) (79)

Rifampicin stimulates warfarin metabolism.

**Anticoagulant/cardiac  
depressant**  
quinidine salts  
(bisulphate, gluconate,  
sulphate) (9, 18, 79)

Quinidine is cumulative in its action and may reduce the synthesis of clotting factors thereby potentiating the action of coumarin and indandione anticoagulants.

**Anticoagulant/  
cimetidine (Tagamet)  
(80–91)**

Studies in normal subjects and in patients have shown that cimetidine interacts with stabilized warfarin regimens to increase blood clotting ratio and prothrombin by about 20%; plasma warfarin concentrations almost doubled. Mechanisms have been

<i>Combination</i>	<i>Interaction</i>
	attributed to inhibition of warfarin metabolism (80–87).
	One controlled study investigated the effects of cimetidine in a large population of patients receiving stable warfarin regimens. The effect of two dosage regimens of cimetidine (300 mg qds or 800 mg daily at bedtime for 15 days) was determined in a cross-over study on prothrombin time ratios (PTRs) of 27 patients stabilized on conservative warfarin regimens giving a PTR of 1.2–2.0.
	The PRT increased with both cimetidine regimens, although the mean PRT remained within current recommendations for anticoagulation. The mean PRT after stabilization on cimetidine ranged from 1.65 to 1.75 for the 800-mg dose at bedtime, and from 1.70 to 1.82 for the 300-mg × 4/day regimen. Only two patients achieved prothrombin times (PTs) of 30 sec (upper limit of desired anticoagulation), and the maximum PT was 30.5 sec. Warfarin AUCs increased significantly with either regimen (39% for × 4/day and 21% for bedtime administration). The addition of the two regimens of cimetidine dosage to a stabilized warfarin regimen did not lead to any serious degree of anticoagulation, despite decreased warfarin clearance. None-the-less, cimetidine did increase PTRs and serum warfarin concentrations, so the prothrombin time should be monitored when cimetidine is added to anticoagulant therapy (88). Cimetidine interacts with the R but not the S isomer of warfarin (89–91).
ranitidine (92)	In contrast ranitidine does not affect the anticoagulant action of warfarin, since it is without an inhibitory effect on hepatic P450 enzyme systems (92).
phenprocoumon/ cimetidine (93)	Cimetidine (400 mg bid) given to 10 patients taking phenprocoumon (9–22.5 mg/week) did not affect anticoagulant control or plasma phenprocoumon levels (93). Phenprocoumon is excreted predominantly after glucuronidation, thus cimetidine, which acts upon

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulant/ cimetidine cont.</b>	mixed functional oxidase systems in the liver, does not influence this metabolism. It was suggested that cimetidine can be combined with phenprocoumon without increasing the risk of bleeding complications (93).
<b>Anticoagulant/ clofibrate (9, 11, 18, 20)</b>	Clofibrate may enhance the effect of coumarin anticoagulants by increased receptor site affinity.  If concomitant use is envisaged the anticoagulant dosage should be reduced, clofibrate introduced and then the anticoagulant dose should be readjusted.
	This interaction is likely with all fibrate cholesterol lowering agents.
<b>Anticoagulant/ corticosteroid (18)</b>	Corticosteroid therapy reportedly increases anticoagulant requirements; corticosteroids can induce gastric ulceration with copious haemorrhage in anticoagulated patients.  Initiation of corticosteroid dosage should be avoided while the patient is anticoagulated.
<b>Anticoagulant/danazol (94–100)</b>	Treatment with danazol (200 mg bd) for 3 weeks caused loss on anticoagulant control in a formerly stabilized patient receiving long-term anticoagulation with warfarin (5 mg daily). She was hospitalized due to haematemesis and abdominal distension; her prothrombin time was 168 sec (test:control ratio, 14:1) (94).  There are other reports of bleeding complications associated with the commencement of danazol in patients stabilized on warfarin (95–97). The mechanism(s) underlying this interaction is uncertain. Firstly, danazol may displace warfarin from plasma albumin binding sites increasing the proportion of free warfarin in the plasma, although this effect would be transient due to the enhancement of hepatic

<i>Combination</i>	<i>Interaction</i>
	metabolism of warfarin. Secondly, it is possible that danazol inhibits the metabolism of warfarin and thus potentiates its action. It is known, for example that danazol potentiates the anticonvulsant carbamazepine by such a mechanism (98, 99). Thirdly, danazol is thought to increase the plasma concentrations of several clotting factors and also of the endogenous anticoagulants, antithrombin III and protein C (100).
	Thus it is possible that the combination of warfarin, which inhibits the synthesis of vitamin K-dependent clotting factors, and danazol, which enhances the activity of endogenous anticoagulants, leads to an increase in warfarin sensitivity. Possibly all three types of mechanisms are involved (97).
<b>Anticoagulant/ disulfiram</b>	Disulfiram is known to augment the hypoprothrombinaemic effects of warfarin (101). It is now established that it acts by interacting primarily with S-warfarin (102). Disulfiram did not change the plasma concentrations of either enantiomorph, so it may augment the anticoagulant effect of racemic warfarin by directly affecting the hepatic mechanism responsible for the hypoprothrombinaemia (102).
<b>Anticoagulant/diuretic ethacrynic acid (20, 31)</b>	Ethacrynic acid displaces warfarin from plasma binding sites. The presence of hypo-albuminaemia or renal insufficiency enhances the amount of warfarin displaced.
	Although this interaction is based on <i>in vitro</i> data, there is some clinical evidence to indicate that reduction in anticoagulant dosage may be necessary.
combinations of diuretics with spironolactone (11)	Anticoagulant control very brittle; frequent changes of coumarin dosage required to maintain steady reduction in prothrombin time.
	Patients on combinations of diuretics which include spironolactone require frequent monitoring of prothrombin time.

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulants/food supplements, vegetables and herbal drugs (103–109)</b> e.g. Gon Isocal broccoli herbal tea	Any substance containing large amounts of vitamin K will, if taken in sufficient amount, antagonize the effect of anticoagulants. A patient with mitral stenosis satisfactorily maintained on dicoumarol had a clotting ratio which fell from the therapeutic range to normal 2 days after commencing Gon which contains vitamin K <sub>4</sub> . A patient maintained on warfarin 8 mg daily required enteral nutrition and the clotting ratio fell, requiring an increase in warfarin to 13 mg daily. The warfarin dosage returned to 8 mg daily after the food supplement was stopped. It is suggested that problems with anticoagulation control are likely when patients take in excess of 6.3 mg of phytomenadione per 1000 kcal (105). Problems have been encountered with patients eating 1 lb of broccoli per day (106) and taking herbal tea (107).
	Ingestion of large amounts of vitamin K in a vegetable-rich weight-reducing diet (1277 µg vitamin K daily) caused resistance to warfarin therapy in one patient. Change to a regular diet (360 µg vitamin K daily) resulted in substantial reduction in warfarin resistance (110).
	Patients on anticoagulants should not embark on weight-reducing diets without first discussing this with their doctor; vegetable-rich diets should be avoided.
	Patients with myocardial infarction are often advised to lose weight and are often anticoagulated. Dieticians are frequently unaware of this interaction and should be informed.
<b>Anticoagulant/hypnotic or sedative barbiturates (9, 11, 18, 20, 111)</b>	Metabolism of coumarin anticoagulants is accelerated due to barbiturate-induced metabolic enzyme induction. Therefore larger doses of anticoagulant are required. A patient on such a combination who stops taking barbiturates runs the risk of haemorrhagic episodes unless the dose of anticoagulant is adjusted (11). Barbiturates may also decrease gastrointestinal absorption of anticoagulants.

<i>Combination</i>	<i>Interaction</i>
	No barbiturate should be started or stopped in a patient on oral anticoagulants without careful readjustment of anticoagulant dosage. The use of chlordiazepoxide or diphenhydramine is a safer alternative to a barbiturate.
chloral hydrate and related compounds; chloral betaine, dichloralphenazone (20, 112-114)	Chloral hydrate and related compounds displace coumarins from plasma protein binding sites and therefore initially may potentiate their anticoagulant effect. However, they increase the metabolism of coumarins by induction of hepatic microsomes and therefore subsequently reduce their anticoagulant effect.
ethchlorvynol (115, 116) glutethimide (9, 18, 20)	These hypnotics increase the rate of metabolism of coumarin anticoagulants due to induction of hepatic microsomes.
<b>Anticoagulant/ influenza vaccine (109, 117, 118)</b>	<p>One patient who had been stabilized on warfarin for 12 years was hospitalized 10 days after influenza vaccination with a massive upper gastrointestinal tract haemorrhage and a prothrombin time of 48 sec. No other cause for the augmented anticoagulation could be identified. It was concluded that influenza vaccine resulted in decreased inactivation of warfarin due to depression of the mixed-function oxidase system which metabolizes warfarin in the liver.</p> <p>Caution should be exercised in giving such patients influenza vaccine and changes in their warfarin requirement should be carefully monitored.</p> <p>More recently a study in elderly subjects showed that clinically significant reactions to warfarin were rare after influenza vaccinations and were no more frequent than in those not receiving vaccinations.</p> <p>Seven elderly subjects on warfarin showed no change in their prothrombin or partial thromboplastin times following influenza vaccination. Others have found no effect of influenza vaccine on theophylline clearance in</p>

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulant/ influenza vaccine <i>cont.</i></b>	normal subjects nor in those with chronic obstructive airways disease.
<b>Anticoagulant/ interferon</b>	Increased anticoagulation was observed in a patient with chronic hepatitis C, who was given human lymphoblastoid interferon $\alpha$ (6.0 MU/day) while taking warfarin after heart surgery. Her maintenance dose of warfarin had previously alternated between 3.5 and 2.5 mg daily. Before starting on interferon, she showed a prothrombin time of 16.7 (INR = 1.60), a Thrombotest result of 27% and a serum warfarin concentration of <0.8 $\mu$ g/ml. After 2 weeks of treatment with interferon, her prothrombin time increased to 20.4 (INR = 1.99), Thrombotest results decreased to 17% and warfarin concentrations rose to 5.2 $\mu$ g/ml. Her warfarin dose was reduced stepwise to 2.0 mg/day and some weeks later anticoagulation and serum warfarin concentrations had returned to nearly their initial values (119). The authors of this report have also had to decrease the dose of warfarin in four patients, two taking interferon $\beta$ , and two taking interferon $\alpha_{2b}$ concomitantly with warfarin (119).
	Interferon does not directly affect the coagulation system, but it is known to inhibit hepatic microsomal enzymes (120, 121), thus the potentiation of warfarin's activity is likely to be the result of a decrease in its hepatic metabolism.
<b>Anticoagulant/ ion-exchange resin cholestyramine (11, 122)</b>	Hypoprothrombinaemia with bleeding due to failure of intestinal absorption of vitamin K has been described in the absence of anticoagulants, thus concomitant therapy with anticoagulants might precipitate a worsening condition. Potential interaction is further complicated by results of animal studies which show that cholestyramine may bind warfarin in the intestine and so delay its absorption.
<b>Anticoagulant/liquid paraffin (123)</b>	Liquid paraffin decreases the intestinal absorption of lipid-soluble materials including vitamin K. Decreased

<i>Combination</i>	<i>Interaction</i>
methyl salicylate ointment	vitamin K absorption enhances the effect of oral anticoagulants.
	A woman maintained for 5 years on warfarin (4–5 mg/day) for a mitral valve replacement, was prescribed methyl salicylate ointment for painful osteoarthritis in both knees. After 2 weeks, she had extensive bruising and her INR had increased from 2.0–3.0 to 6.09. Her blood salicylate level was 2.5 mmol/l. She was hospitalized and transfused with 3 units of fresh frozen plasma and her INR fell to 3.5. She was discharged and told not to use the ointment (124). It is known that salicylates depress prothrombin formation in the liver and also displace warfarin from protein binding sites and thus increase the risk of bleeding (18). However, this has always tacitly been thought to apply only with systemic dosage; this case clearly shows that topical methylsalicylate, an over-the-counter item, should not be used by patients taking warfarin.
<b>Anticoagulant/oral contraceptive (125–127)</b>	Oral contraceptives increase the synthesis of specific blood coagulation factors; this may impair the efficacy of anticoagulant therapy. This interaction may be of importance in anticoagulating women with deep vein thromboses, caused by oral contraceptive medication, since higher doses of anticoagulant may be required for some days even after stopping the contraceptive.
phenprocoumon (128)	The long-term use of oral contraceptives (combined type, low-dose oestrogen) in seven healthy women was associated with a significant increase in the clearance of the anticoagulant phenprocoumon when compared with a control group of women not taking OCs. Mean values of AUC and $t_{1/2}$ values were significantly lower in the OCs users (128). The mechanism involved is thought to be accelerated glucuronidation of the anticoagulant by the OC.
	Although women who require anticoagulants do not advisedly use oral contraceptives, it may be necessary to have reliable contraception in women being treated

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulant/oral contraceptive cont.</b>	with an anticoagulant, if an intra-uterine device is not acceptable. Careful monitoring of the anticoagulant effect of treatment is therefore essential.
	Paradoxically, oral contraceptives have also been reported to potentiate the action of anticoagulants in some patients. <i>In those patients with oral contraceptive-induced thrombosis, the oral contraceptive agent must be discontinued.</i>
<b>Anticoagulant/proton pump inhibitors (20)</b>	Omeprazole can delay the elimination of warfarin due to inhibition of hepatic metabolism
<b>Anticoagulant/quinine salts (18, 20)</b>	Quinine may depress the formation of prothrombin in the liver and enhance the effect of anticoagulants.
<b>Anticoagulant/silicones (129)</b>	Simethicone (activated dimethicone; e.g. Asilone, Diloran) impairs warfarin absorption.
<b>Anticoagulant/sulphipyrazone (Anturan) (130–136)</b>	The anticoagulant effect of warfarin is potentiated by the platelet inhibitor sulphipyrazone (130–134). Plasma protein binding displacement of warfarin has been suggested as the mechanism of interaction (130, 131), although other mechanisms may be involved in view of the sustained reduction of warfarin requirements during sulphipyrazone treatment (132). Sulphipyrazone has been shown to have a stereoselective effect in reducing metabolic clearance of the S-warfarin enantiomorph (135). Prolonged treatment with sulphipyrazone in one patient caused a biphasic interaction with warfarin potentiation followed by antagonism. The likely mechanism of this biphasic interaction is initial displacement of warfarin from albumin binding sites followed by its enhanced hepatic metabolism (134). A recent report described how sulphipyrazone caused a rapid increase in the prothrombin ratio in five patients and the warfarin

<i>Combination</i>	<i>Interaction</i>
	dose had to be reduced by a mean of 46% to maintain the PT ratio in the therapeutic range (136).
<b>Anticoagulant/ tamoxifen</b>	This is a clinically important interaction which can cause life-threatening haematemesis and melaena (131), due to its rapid and marked effect on the PT ratio. Warfarin dose should be reduced by half and the patient frequently monitored if sulphapyrazone is started during warfarin therapy. By contrast, in patients already receiving both drugs, warfarin dose will need to be increased if sulphapyrazone is stopped (136).
<b>Anticoagulant/thyroid hormones</b> dextrothyroxine sodium (142–144) e.g. di-iodotyrosine liothyronine sodium thyroxin sodium	The Committee on Safety on Medicines have received two reports of serious over-anticoagulation when tamoxifen was used in combination with warfarin. Considerable reductions in the daily dose of warfarin were required to maintain safe anticoagulation (137). A further five cases where the interaction was life-threatening with marked prolongation of prothrombin times, haematuria, and haematoma have been reported in women taking tamoxifen who were then started on warfarin to treat deep vein thrombosis or pulmonary embolism (138–140).  Peliosis hepatis and fatal liver haemorrhage have been reported in a patient who was receiving tamoxifen with warfarin and a thyroxine-liothyronine preparation (141). It has been suggested that, in addition to enhancement of the effects of warfarin, competition for the same metabolic enzyme systems might reduce the activity of tamoxifen against tumours, but such a suggestion remains speculative (139).

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulant/thyroid hormones cont.</b>	when thyroid replacement was begun in the presence of long-term warfarin therapy (146). The mechanism of this potentiation is thought to be an increased receptor site affinity.
	A reduced anticoagulant dosage requirement should be anticipated.
<b>Anticoagulant/tranquilliser</b> benzodiazepines (147, 148) e.g. chlordiazepoxide diazepam medazepam oxazepam	Benzodiazepines have been shown in the clinic not to interfere with the anticoagulant action of coumarin derivatives; it appears safe to prescribe these agents to patients on long-term oral anticoagulants. A complex interaction between benzodiazepines and coumarins takes place in digitalized patients (11).
	The benzodiazepine tranquillisers are drugs of choice when a sedative or hypnotic is required.
<b>Anticoagulant/vitamin K</b>  weight-reducing diets rich in vitamin K	Phytomenadione is a naturally occurring vitamin K which maintains a normal concentration of prothrombin in the blood plasma. It has largely replaced the other compounds as an antidote to oral anticoagulants since it has a rapid and prolonged action. It is available in injection and oral dosage forms. <i>It is not an antidote to heparin.</i>
	Ingestion of large amounts of vitamin K in a vegetable-rich weight-reducing diet (1277 µg vitamin K daily) caused resistance to warfarin therapy in one patient. Change to a regular diet (360 mg vitamin K daily) resulted in substantial reduction in warfarin resistance (149).
<b>Anticoagulant/xanthine oxidase inhibitors</b> allopurinol (Aluline,	Decreased rate of coumarin metabolism. Control of anticoagulant therapy is very brittle. Avoid use of coumarin anticoagulants in gout patients treated with allopurinol.

<i>Combination</i>	<i>Interaction</i>
Caplenal, Zyloric) (11, 14)	Phenindione is an acceptable alternative anticoagulant.

#### 4. INTERACTIONS WITH INJECTED ANTICOAGULANTS AND THROMBOLYTIC AGENTS

<i>Combination</i>	<i>Interaction</i>
<b>Alteplase/ <math>\beta</math>-adrenergic blocking agents</b> nitrates (150–152)	Acute administration of nitrates and $\beta$ -adrenergic blocking agents produce a decrease in hepatic blood flow (HBF). Therefore these compounds would be expected to decrease the clearance of alteplase by the liver and increase its effect.
<b>Alteplase/calcium antagonists (150–152)</b>	Calcium antagonists increase hepatic blood flow and will increase the hepatic clearance with a reduction in its effect.
<b>Alteplase/nifedipine</b>	Studies were performed in small groups of healthy volunteers. Nifedipine was expected to change the pharmacokinetics of alteplase by increasing the HBF. In the study with nifedipine, the increase in HBF was confirmed by estimation of the apparent HBF by indocyanine green.
<b>Alteplase/epoprostenol</b> (150, 153)	Epoprostenol increases hepatic blood flow and on theoretical grounds could antagonize the action of alteplase.
<b>Alteplase/heparin coumarins (154)</b>	Prior administration of anticoagulants may increase the risk of bleeding. Alteplase is commonly used in conjunction with heparin.
<b>Ancrod/plasma expanders</b>	Artificial plasma expanders, e.g. dextrans, may cause severe bleeding in defibrillated patients and should not be administered during or within 10 days of ancrod therapy (155). Bleeding associated with ancrod should be treated with specific antidote which is available from the manufacturers.

*Combination**Interaction*

<b>Heparin/antidiabetic agent (156)</b> glipizide	Glipizide is a second-generation sulphonylurea and has pharmacokinetic properties which should lessen the risk of hypoglycaemia.
	A case was described of a 64-year-old diabetic stabilized on glipizide 5 mg/day who was given heparin intravenous infusion. He suffered recurring hypoglycaemia attacks over 4 days.
	Sulphonylureas are highly bound to protein and even small doses of heparin decrease indirectly the binding of drugs by increasing free fatty acid concentrations, an effect more pronounced in diabetes than others.
<b>Heparin/protamine</b>	When injected intravenously, protamine sulphate neutralizes the anticoagulant action of heparin and is used to check haemorrhage caused by heparin overdosage. <i>It is not an antidote to the oral anticoagulants.</i>
<b>Heparin/coumarin anticoagulant (157)</b>	The combination of oral anticoagulant and heparin prolongs the prothrombin time.
<b>Streptokinase/drugs affecting platelet function</b>	Drugs which affect platelet adhesiveness, such as aspirin, other salicylates, pyrazolone, or indole derivative, should not be administered concurrently with streptokinase.
	In ISIS-2 (158) it was demonstrated that the addition of aspirin to streptokinase therapy did not further increase the occurrence of major bleeding complications (requiring transfusion and cerebral bleeding). The excess of minor bleeding complications caused by streptokinase was slightly greater in the presence of aspirin (2.8% compared with 2.3% in the absence of aspirin).
<b>Streptokinase/heparin (158–163)</b>	If heparin or coumarin anticoagulants have been given before commencing streptokinase therapy further administration should cease (it is not advisable to give streptokinase and heparin simultaneously). If

*Combination**Interaction*

immediate treatment with streptokinase is required heparin should be neutralized with protamine sulphate.

In ISIS-2 the excess of bleeds during streptokinase was increased by heparin (2.6 vs. 1.5% for minor bleeds and 0.4 vs. 0.0% for major bleeds). In GISSI-2 (160) and ISIS-3 (159) the addition of heparin to aspirin plus a thrombolytic agent increased the occurrence of major bleeds from 0.5 and 0.8%, respectively to 1.0%.

**Streptokinase/  
traxenamic acid (161)**

Traxenamic acid 10 mg/kg body weight by slow intravenous infusion will neutralize the effects of streptokinase in the event of haemorrhage.

**Recommended further reading**

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## **2.4 DRUG INTERACTIONS WITH LIPID LOWERING AGENTS**

Lipid-lowering agents should be reserved for patients with coronary artery disease and for those with a high risk of developing coronary artery disease on account of multiple risk factors, which include severe hyperlipidaemia inadequately controlled by diet. It is pointless to treat patients with hypolipidaemic agents unless dietary advice is given and adhered to and steps taken to cease smoking.

Severe hyperlipidaemia may require treatment with combinations of lipid-lowering agents in addition to adherence to a strict low fat diet. Combinations of HMG CoA reductase inhibitors with nicotinic acid or a fibrate carries a high incidence of side effects. As a group it is probable that there is considerable inappropriate prescribing since these agents should be used for *specific* hyperlipidaemia types. It is also likely that they are over prescribed since all too often dietary measures are not given adequate trial.

### **ANION EXCHANGE RESINS**

Cholestyramine

Colestipol

Polidexide

Indications for use are WHO type IIa hyperlipidaemia. Other medication should be taken 1 hr before or 4–6 hr after anion exchange resins which can reduce their absorption.

### **CLOFIBRATE TYPE**

Beclofibrate

Bezafibrate

Ciprofibrate

Clofibrate

Fenofibrate

Gemfibrozil

Pirifibrate

Plafibrate

The fibrate group can be regarded as ‘broad spectrum’ lipid-altering drugs. Their main action is to reduce triglycerides and low-density cholesterol (LDC) and raise

high density cholesterol (HDL). Bezafibrate, fenofibrate, and gemfibrozil can be used to treat type IIa, IIb, III, IV and V hyperlipidaemias, ciprofibrate is not regarded as ideal for type V, nor is clofibrate regarded as suitable for type II a hyperlipidaemia.

There is an increased incidence of cholesterol gall bladder stones in patients treated with this group of lipid-lowering drugs. Bezafibrate has produced liver tumours in female rats (1). Clofibrate (2) has been shown to produce liver tumours in rats and mice. In man, liver enzyme changes, liver dysfunction and hepatomegaly have been reported.

### **NICOTINIC ACID DERIVATIVES**

Acipimox  
Nicofuranose  
Nicotinic acid

Nicotinic acid and derivatives are used in Types IIa, IIb and IV hyperlipidaemia.

Doses of this group of agents is 1.5–3.0 gm per day. *Side effects* are vasodilation, flushing, palpitations, headache, pruritis, rashes, gastric irritation with nausea and vomiting, diarrhoea. Anaphylactoid reactions have been reported. *Contraindications* are peptic ulceration or pregnancy.

### **PROBUCOL**

Probucol is the only member of this group and decreases both LDL and HDL cholesterol. It promotes resolution of cholesterol xanthomata. Probucol has been reported to cause angioneurotic oedema. Fatal cardiac arrhythmias have been reported in animal studies and prolonged QT intervals in man. It should not be administered to patients with recent myocardial damage. The risk of arrhythmias is increased in patients who are also taking tricyclic antidepressants or class I or III antiarrhythmic agents or phenothiazines.

### **HMG CoA REDUCTASE GROUP**

Lovastatin  
Mevastatin  
Pravastatin  
Simvastatin

Lovastatin, the first member of this group, was originally extracted from *Aspergillus terreus*. These agents competitively inhibit 3-hydroxy-3-methylglutaryl Co-enzyme A (HMG CoA) reductase, an enzyme that catalyzes a step in cholesterol synthesis in the liver. They are more potent than anion exchange resins in lowering LDL

cholesterol but less effective than the clofibrate group of drugs in reducing triglycerides.

The main side effect is myalgia and rhabdomyolysis. This complication is more common in patients receiving an HMG CoA reductase inhibitor in conjunction with a fibrate or nicotinic acid derivative.

Simvastatin has been found to cause small reductions in cortisol synthesis.

Proteinuria has also been described in patients receiving the 'statin' group of hypolipidaemic agents (3).

Simvastatin has also been shown to be porphyrogenic in animals and in *in vitro* systems. It should not be given to patients with porphyria (4).

Lens opacities were found in 13 of 101 patients taking part in an 18-week study of lovastatin (5), but there was no deterioration in 11 of these patients after 26 months. Other studies have failed to confirm this adverse effect.

### **OMEGA-3 MARINE TRIGLYCERIDES**

Fish oils rich in omega-3 marine triglycerides are claimed to be effective in the treatment of severe triglyceridaemia. Paradoxically it can cause marked increases in plasma cholesterol. There is some doubt as to whether the hypertriglyceridaemic effect is sustained during long-term therapy.

### **SQUALENE SYNTHETASE INHIBITORS**

New approaches to lipid lowering includes the development of squalene synthetase inhibitors. Squalene is a precursor not only in the synthesis of cholesterol but also of steroid hormones.

### **ACAT AND CETP INHIBITORS**

Specific inhibitors of these enzymes are under development.

### **MUSCLE DAMAGE ASSOCIATED WITH LIPID-LOWERING DRUGS**

Muscle disorders are well recognized with lipid-lowering agents of the fibrate group, e.g. bezafibrate, ciprofibrate, clofibrate, gemfibrozil and fenofibrate, and of the HMG CoA reductase group, e.g. prevastatin, simvastatin and fluvastatin. Rhabdomyolysis appears to be rare with an incidence of one case per 100,000 treatment years.

The risk of muscle toxicity is greatly increased in patients with renal impairment, or hypothyroidism. Combined treatment with a fibrate and an HMG CoA reductase inhibitor *greatly* increases the risk of muscle damage. There also appears to be a serious risk of muscle damage if an HMG CoA reductase inhibitor or a fibrate are given concurrently with cyclosporin.

<i>Combination</i>	<i>Interaction</i>
<b>ANION EXCHANGE RESINS</b>	
<b>Thiazide diuretics/ Propranolol/ Tetracyclines/ Thyroxine/anion exchange resins (6–9)</b>	There is reduced absorption of a wide range of medicines, particularly acidic drugs, caused by cholestyramine, colestipol and other lipid-lowering agents of this class. Enterohepatic circulation may be reduced. Medications should be taken 1 hr before or 4–6 hr after these agents.
<b>Anticoagulants/anion exchange resins (10, 11)</b>	The effect of anion exchange resins on the anticoagulant effect of warfarin (12), nicoumalone, or phenidione may be to reduce or enhance the effect. This depends on whether the greatest impairment of absorption is on the anticoagulant or vitamin K.
	Cholestyramine and colestipol impair the absorption of fat and fat-soluble vitamins A, D, E and K. Chronic use of cholestyramine may be associated with hypoprothrombinaemia associated with vitamin K deficiency, and this has led to increased bleeding tendency (13).
<b>Acarbose/anion exchange resins (6, 7, 8)</b>	The hypoglycaemic effect of acarbose is enhanced by cholestyramine.
<b>Dietary fat/anion exchange resins (8)</b>	Cholestyramine may cause fatty diarrhoea (steatorrhoea) due to reduced absorption of fat and bile salts.
<b>Vitamins/anion exchange resins (8)</b>	Absorption of fat-soluble dietary vitamin is grossly impaired. Vitamin supplementation may be necessary.
<b>CLOFIBRATE GROUP</b>	
<b>Anticoagulants/ Phenytoin/ Sulphonylurea oral/ Hypoglycaemics/ clofibrate group (1, 2, 14, 15)</b>	Clofibrate displaces acidic drugs from plasma protein binding sites and thereby potentiates their effects. Patients taking anticoagulants should in general have their anticoagulant dosage halved if clofibrate is to be co-administered. Patients on oral sulphonylurea hypoglycaemics, e.g. tolbutamide have been reported to develop hypoglycaemia when treated with fibrate agents. Co-administration of the fibrate group of

<i>Combination</i>	<i>Interaction</i>
<b>HMG CoA reductase inhibitor/clofibrate group (1, 14, 16)</b>	hypolipidaemic agents with phenytoin has led to phenytoin toxicity.
<b>Anion exchange resin/gemfibrozil (14)</b>	There is an increased risk of myalgia, myopathy and rhabdomyolysis when lipid-lowering agents of these two types are co-administered.
<b>Colestipol/gemfibrozil (17)</b>	The bioavailability of gemfibrozil is reduced when co-administered with cholestyramine type hypolipidaemic agents. If both types of agent are to be used to treat hyperlipidaemia they should be taken 4–6 hr apart.
<b>Warfarin/gemfibrozil (18)</b>	Gemfibrozil has been reported to enhance the effects of warfarin.
<b>NICOTINIC ACID DERIVATIVES</b>	
<b>Anion exchange resin/acipimox (19, 20)</b>	Cholestyramine does not affect the absorption of acipimox, it enhanced hypolipidaemic effects.
<b>Alcohol/acipimox (19)</b>	Patients taking acipimox should avoid alcohol.
<b>Aspirin/nicotinic acid derivatives (6)</b>	The flushing caused by nicotinic acid derivative can be reduced by taking 75 mg aspirin 30 min before. The flushing is thought to be prostaglandin mediated.
<b>PROBUCOL</b>	
<b>Phenothiazines/tricyclic antidepressants/class I and III anti-arrhythmic/agents/probucol (21–25)</b>	Probucol can induce cardiac arrhythmias, it increases the QT interval. The risk of a probucol-associated dysrrhythmia is enhanced by phenothiazines, tricyclic antidepressants, and Class I and III anti-arrhythmic agents.

*Combination**Interaction***HMG CoA REDUCTASE INHIBITORS**

**Anticoagulants/  
simvastatin pravastatin  
(1)  
lovastatin (26)**

The anticoagulant effects of warfarin and nicoumalone are enhanced. Hypoprothrombinaemia and bleeding has been reported in patients on warfarin given lovastatin.

**Cyclosporin/  
simvastatin (27)  
pravastatin (28)  
lovastatin (29, 30, 31)**

Increased risk of myalgia, myositis and rhabdomyolysis. There have been a number of reports of myopathy and rhabdomyolysis in patients receiving immunosuppressant therapy following transplant surgery on lovastatin.

**Erythromycin/  
lovastatin (32)**

Reports of myopathy and rhabdomyolysis being accentuated by erythromycin given in combination with lovastatin exist.

**Lipid-lowering agents/  
simvastatin (27)  
pravastatin (28)**

Increased risk of muscle damage when a 'statin' type hypolipidaemic agent is coadministered with a 'fibrate' type of lipid-lowering drug.

**Lovastatin (33, 34)**

Increased risk of muscle damage exists when lovastatin has been administered in combination with gemfibrozil (33, 34) and nicotinic acid (35).

**Thyroxine/simvastatin  
pravastatin (36, 37)**

This group of drugs has been associated with the development of both hyperthyroidism and hypothyroidism in patients on thyroxine.

**OMEGA-3 TRIGLYCERIDES**

**Anticoagulants/  
maxepa (28)**

Omega-3 triglycerides have antithrombotic activity and should be given with caution to patients with haemorrhagic disorders or on anticoagulants.

**Antidiabetic  
agents/maxepa  
(39–43)**

A deterioration in control of blood sugar has been reported in both insulin- and non-insulin-dependent diabetics.

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## **2.5. DIURETICS**

### **INTRODUCTION**

Diuretics promote the excretion of water and electrolytes by the kidneys. They are used in the treatment of heart failure or in hepatic, renal, or pulmonary disease when salt and water retention has resulted in oedema or ascites. Diuretics are used either alone or in combination with other agents in the treatment of hypertension. There are undoubtedly too many diuretics available, especially within the thiazide group. The major groups of diuretics are as follows:

### **1. THIAZIDE (BENZOTHIAZIDE) AND STRUCTURALLY RELATED DIURETICS:**

althiazide	indapamide
bemetizide	mebutizide
bendrofluazide	mefruside
benzylhydrochlorothiazide	methylclothiazide
buthiazide	meticrane
chlorothiazide	metolazone
chlorthalidone	paraflutizide
clopamide	penflutizide
clorexolone	polythiazide
cyclopenthiazide	quinethazone
cyclothiazide	teclothiazide
epithiazide	trichlormethiazide
hydrochlorothiazide	tripamide
hydroflumethiazide	xipamide

They are moderately potent diuretics which inhibit sodium and chloride reabsorption at the beginning of the distal convoluted kidney tubules and produce a corresponding increase in potassium excretion.

Prolonged administration may produce hypokalaemia, the magnitude of the K<sup>+</sup> deficit is often underestimated especially in geriatric patients who may be K<sup>+</sup> depleted because of a simple lack of intake even before diuretic treatment is begun. Diuretic-induced hypokalaemia intensifies the cardiac effect and toxicity of digoxin and related cardiac glycosides. Thiazides may provoke hyperglycaemia and glycosuria in diabetics and other susceptible patients; they may also cause hyperuricaemia and precipitate attacks of gout.

**2. LOOP (OR 'HIGH-CEILING') DIURETICS:**

<b>azosemide</b>	<b>frusemide (furosemide)</b>
<b>bumetanide</b>	<b>muzolimine</b>
<b>ethacrynic acid</b>	<b>piretanide</b>
<b>etozolin</b>	<b>torasemide</b>

They produce an intense dose-dependent diuresis of relatively short duration and they may be effective where thiazides have failed. They have similar adverse effects to the thiazides, and in addition may cause tinnitus and deafness (e.g. ethacrynic acid (1–3), frusemide (4)) especially in patients with renal insufficiency. Early reports suggested that bumetanide might be less ototoxic than frusemide (5). However, both drugs can cause deafness especially when given in large doses to patients with renal impairment. Although ethacrynic acid is generally considered to have less pronounced effects on carbohydrate metabolism than frusemide or the thiazides, reductions in glucose tolerance have been reported (6–8). Frusemide and ethacrynic acid may enhance the nephrotoxicity or ototoxicity of other drugs particularly in patients with renal impairment.

**3. POTASSIUM-SPARING DIURETICS:**

<b>amiloride</b>	<b>spironolactone</b>
<b>canrenoate potassium</b>	<b>triamterene</b>
<b>canrenone</b>	

They have a relatively weak diuretic effect and are used in conjunction with thiazides or loop diuretics. Spironolactone is a steroid having close structural similarity to aldosterone; it acts as a competitive inhibitor of aldosterone and therefore increases  $\text{Na}^+$  and reduces  $\text{K}^+$  excretion in the distal renal tubules. It has a slow and prolonged action and can be combined with other diuretics, usually thiazides.

Canrenone has similar actions and use to those of spironolactone; the potassium salt is a soluble form of canrenone and is suitable for parenteral administration. Amiloride and triamterene also diminish the excretion of  $\text{K}^+$  and are used in combination with other diuretics to counteract their  $\text{K}^+$  depleting effects.

**4. OSMOTIC DIURETICS:**

<b>isosorbide</b>
<b>mannitol</b>
<b>urea</b>

They raise the osmality of plasma and tubular fluid. They are rarely used in heart failure as they may acutely expand the blood volume. Mannitol is used in cerebral oedema.

**5. MERCURIAL DIURETICS:****mersalyl sodium**

They are effective diuretics but are now rarely used because of their nephrotoxicity; mersalyl must be given by i.m. injection, i.v. use may cause severe hypotension and sudden death.

**6. CARBONIC ANHYDRASE INHIBITORS:****acetazolamide****dichlorphenamide****dorzolamide****methazolamide**

They are weak diuretics and are used mainly to treat raised intraocular pressure. They inhibit the ion-exchange in the renal tubules which is catalysed by the enzyme carbonic anhydrase. They thus increase the excretion of cations, chiefly  $\text{Na}^+$  and  $\text{K}^+$ , and by doing so promote diuresis.

Interactions between diuretics and other diuretics are summarized in the following Table of Drug Interactions; for a general review of interactions, including useful interactions, between diuretics and other drugs, see the review article by Crook and Nies (9).

<i>Combination</i>	<i>Interaction</i>
<b>Diuretic/anticoagulant (10, 11)</b>	There have been a number of studies on the effects of diuretics on anticoagulants; tienilic acid (now withdrawn) produced the most serious interaction, enhancing the activity of ethylbiscoumacetate (12), nicoumalone (13), and warfarin (14) and has led to haemorrhage. Ethacrynic acid enhances the effects of warfarin (15) although not to the same severe effect as tienilic acid. Chlorthalidone (16) and spironolactone (17) have both been associated with a reduction of warfarin's activity in healthy subjects, and it has been suggested that this might be due to the diuresis concentrating the circulating clotting factors. However, bumetanide, frusemide and the thiazides do not appear to affect the actions of warfarin.
<b>Diuretic/antidiabetic</b>	Thiazides (18), ethacrynic acid (18), frusemide (19), and triamterene (19) have long been known to elevate the blood sugar level in diabetics and prediabetics. They antagonize the action of antidiabetic drugs especially the sulphonylureas. The mechanism is

<i>Combination</i>	<i>Interaction</i>
<b>Antidiabetic cont.</b>	thought to be partly due to K <sup>+</sup> loss induced by the diuretic. Depression of pancreatic islet tissue may also be involved (20). Diabetic patients receiving diuretics should be carefully monitored for possible decreased diabetic control. If necessary, a less diabetogenic diuretic should be substituted and potassium supplementation may be helpful.
<b>Diuretic/corticosteroid</b>	K <sup>+</sup> -losing diuretics given together with corticosteroids may enhance the total K <sup>+</sup> loss. This combination may result in severe K <sup>+</sup> loss and the patients electrolyte balance must be carefully monitored (21). (See also thiazide/corticosteroid interaction below.)
<b>Diuretic/lithium</b>	Amiloride and other K <sup>+</sup> -sparing diuretics have no effect on lithium excretion, but acetazolamide may increase lithium excretion, transiently (22) Diuretic-lithium interactions and the precautions to be observed have been reviewed (23). Thiazide diuretics produce sodium depletion by inhibiting distal tubular sodium reabsorption. The consequent increase in proximal tubular reabsorption frequently results in an increase in plasma lithium concentrations (22) with a risk of toxicity (24, 25).  Loop diuretics (bumetanide, ethacrynic acid, frusemide) seem less likely to cause lithium retention, although caution is warranted especially in patients on dietary sodium restrictions (22, 25). It has been suggested that if diuretic therapy is necessary in patients stabilized on lithium, a reduction of 25–50% of the lithium dose should be initiated together with twice weekly monitoring until re-stabilized (22, 25, 26) and that loop-diuretics would be preferable.
<b>Diuretic/NSAID (27–33)</b>	There are an increasing number of reports of interactions between diuretics and NSAIDs. They decrease the diuretic and hypotensive effect of the diuretic. It has been suggested that the mechanism involved may be the interference with the production of renal prostaglandins which are required to mediate the action of diuretics. This appears to be a class effect

<i>Combination</i>	<i>Interaction</i>
	of the NSAIDs. (See entries below under frusemide, thiazides and triamterene.)
	The attenuation of diuresis is an important clinical effect which is capable of inducing cardiac failure and negating the hypotensive effects of diuretics. NSAIDs are therefore generally contraindicated in patients requiring diabetic therapy.
<b>Diuretic/ trimethoprim</b>	There are reports of severe hyponatraemia in patients taking trimethoprim with co-amiloride (34) or hydrochlorothiazide (35).
<b>Acetazolamide/lithium</b>	Acetazolamide impairs the proximal tubular reabsorption of lithium and increases its renal excretion. This increased lithium excretion could impair the antipsychotic effect of lithium (36). Lithium and acetazolamide should not be given together; if such a combination is necessary, the dose of lithium should be increased to compensate for the increased lithium excretion and to maintain a satisfactory antipsychotic effect. Alternative diuretics, thiazides and triamterene also affect lithium excretion but frusemide does not apparently interact with lithium.
<b>Acetazolamide/quinidine</b>	Acetazolamide tends to make the urine alkaline, this results in an increased proportion of un-ionized quinidine. Renal tubular reabsorption of quinidine is thus increased and serum levels may rise, thereby increasing the risk of side effects and toxicity (37–39). Care should always be taken in prescribing urine-alkalinizing agents (this includes sodium bicarbonate) for patients receiving quinidine.
<b>Amiloride/ACE inhibitor, K<sup>+</sup>-sparing drugs and K<sup>+</sup> supplements</b>	There is a risk of hyperkalaemia if amiloride is given in association with an ACE inhibitor. Amiloride should not be given to patients with hyperkalaemia or renal impairment and should not be given with potassium-sparing drugs or potassium supplements (40). Elderly patients and patients with impaired renal function or diabetes melitus are at particular risk of developing hyperkalaemia. It should be given with care

<i>Combination</i>	<i>Interaction</i>
<b>Amiloride/ACE inhibitor, K<sup>+</sup>-sparing drugs and K<sup>+</sup> supplements cont.</b>	to patients likely to develop acidosis, to diabetics, and to those with impaired renal or hepatic function. Amiloride should be discontinued at least 3 days before glucose tolerance tests because of the risks if patients are hyperkalaemic. Serum electrolytes and blood-urea nitrogen should be estimated periodically (40–44).
<b>Amiloride/digoxin</b>	Amiloride increased the renal clearance of digoxin and reduced the extrarenal digoxin clearance in six healthy subjects after a single i.v. dose of digoxin. It also inhibited the digoxin-induced positive inotropic effects, but the clinical implications in cardiac patients are unknown (45).
<b>Amiloride/lithium</b>	Amiloride and other K <sup>+</sup> -sparing diuretics have no effect on lithium excretion, but acetazolamide may increase lithium excretion, transiently (22). Diuretic/lithium interactions and the precautions to be observed have been reviewed (23). (See also entry on diuretic/lithium interactions above.)
<b>Ethacrynic acid/aminoglycoside antibiotic</b>	Ethacrynic acid is ototoxic in its own right and will potentiate the ototoxicity of the aminoglycoside antibiotics and other ototoxic drugs. This effect is most marked in uraemic patients (46, 47). This combination should be avoided; use an alternative diuretic (not frusemide). There is some evidence that the renal toxicity of the aminoglycosides is also enhanced by ethacrynic acid.
<b>Ethacrynic acid/cardiac glycosides</b>	The effect and toxicity of digoxin and other cardiac glycosides are enhanced by hypokalaemia which may follow treatment with the thiazides and other K <sup>+</sup> -losing diuretics (48, 49).
<b>Frusemide/antibiotics</b>	Frusemide may enhance the nephrotoxicity of cephalosporin antibiotics and the ototoxicity of aminoglycosides (50). Clinical reports of transient ototoxicity have followed high-dose i.v. frusemide therapy in patients with diminished renal function. Combinations of frusemide with aminoglycoside

<i>Combination</i>	<i>Interaction</i>
	antibiotics may potentiate the ototoxicity of the antibiotic (See also frusemide/gentamicin interaction below.) This interaction is potentially hazardous and should be avoided; if possible an alternative diuretic (not ethacrynic acid) should be substituted. There is also some evidence that the renal toxicity of the aminoglycosides is also increased by frusemide. (See also review article (51).)
<b>Frusemide/anticonvulsant</b>	The diuretic effect of frusemide is substantially reduced by concomitant antiepileptic therapy (52,53); the mean diuretic effect of oral dosage (20 or 40 mg) was, respectively, 68 and 51% that of controls (52).
<b>Frusemide/antihypertensive</b>	Excessive hypotension can occur when frusemide is used in conjunction with other antihypertensive agents. Particular care should be taken with ACE inhibitors since combination with frusemide can result in marked reduction in blood pressure (54).
<b>Frusemide/carbamazepine</b>	There are reports of symptomatic hyponatraemia associated with the concomitant use of carbamazepine with frusemide or hydrochlorothiazide (55).
<b>Frusemide/chloral hydrate</b>	A syndrome of flushing, tachycardia, raised blood pressure and severe diaphoresis occurred following IV dosage of frusemide to six patients who had received oral chloral hydrate during the preceding 24 hr. (56). The reaction re-occurred in one patient on rechallenge. A subsequent retrospective study (57) among patients who had received both drugs showed that one patient suffered a similar reaction and two had possibly been affected (57). A similar interaction has been reported in an 8-year-old child (58).
<b>Frusemide/gentamicin</b>	Glomerular filtration rate fell significantly after i.v. bolus of frusemide (40 mg) in seven patients; a similar though less marked fall in gentamicin clearance occurred in six of these. Small but consistent increases in plasma gentamicin concentrations were observed after frusemide, and in two patients they rose to within the toxic range (16 and 21 µg/ml, respectively). This

*Combination**Interaction*

<b>Frusemide/gentamicin cont.</b>	reduction in clearance may explain the enhanced risks of nephrotoxicity or ototoxicity in patients receiving both aminoglycosides and diuretics (59). Such a combination should only be used with caution and the patient should be carefully monitored for both renal and auditory functions.
<b>Frusemide/NSAID (flurbiprofen)</b>	Renal osmolal clearance after a standard water load was measured in normal subjects. After flurbiprofen (100 mg orally) the osmolal clearance fell by 29%. After frusemide (40 mg orally or 20 mg i.v.) the osmolal clearance increased by 105 and 140%, respectively, but following treatment with flurbiprofen the corresponding increases in osmolal clearance were only 19 and 90%. This antagonism between a NSAID and a diuretic may occur with other NSAIDs and may be a common and clinically important interaction (60). The patient should be monitored to ensure that diuresis is adequate, if necessary the dose of the diuretic should be increased.
<b>Frusemide/phenytoin</b>	Epileptics being controlled with phenytoin have a diminished response to frusemide (52). Studies in volunteers have shown that the diminished response is due to decreased (up to 50%) intestinal absorption of frusemide; possibly this is related to a phenytoin-induced increase in Na <sup>+</sup> absorption. The dose of frusemide may have to be substantially increased to obtain a satisfactory diuresis.
<b>Frusemide/probenecid</b>	Probenecid reduces the renal clearance of frusemide (61–64) and reduces its diuretic effect (62, 63).
<b>Frusemide/skeletal muscle relaxant</b>	Frusemide may potentiate the effect of tubocurarine and other non-depolarizing muscle relaxants by depleting serum K <sup>+</sup> (65). It is recommended that oral frusemide be discontinued for 1 week and parenteral frusemide for 2 days prior to elective surgery.
<b>Frusemide/theophylline</b>	Frusemide (40 mg by i.v. bolus) caused an average increase of 29 µg/ml in serum theophylline concentrations in ten patients maintained at a steady

<i>Combination</i>	<i>Interaction</i>
	<p>state on a continuous i.v. aminophylline infusion. A reduction in the volume of distribution of theophylline is the most likely mechanism for this interaction. (66). Patients stabilized on a theophylline regimen should be monitored closely during <i>the addition or discontinuation</i> of frusemide therapy.</p>
<b>Metolazone/captopril</b>	Deterioration in renal function occurred in a 65-year-old woman when metolazone (5 mg daily) was added to treatment with captopril, frusemide, spironolactone and digoxin for heart failure. An interaction between captopril and metolazone was suspected and normal renal function returned when both these drugs were stopped. It was suggested that natriuresis and a fall in blood pressure caused by the diuretic might have compromised an already low renal perfusion pressure when autoregulatory mechanisms were blocked by captopril (67).
<b>Metolazone/cyclosporin</b>	An increase in serum creatinine concentration in a renal transplant patient was attributed to a toxic drug interaction between metolazone and cyclosporin. Creatinine concentrations returned to pretreatment levels when metolazone was discontinued (68).
<b>Metolazone/frusemide</b>	Severe electrolyte disturbances may occur in patients given the thiazide diuretic metolazone together with frusemide. The BNF cautions that patients taking this combination should be monitored carefully (69).
<b>Metolazone/glibenclamide</b>	Hypoglycaemia occurred in a diabetic patient, controlled on glibenclamide, 40 hr after initiation of treatment with metolazone (5 mg daily) (70). Studies on protein binding <i>in vitro</i> gave no evidence of displacement of glibenclamide from binding sites.
<b>Spironolactone/ACE inhibitor</b>	Hyperkalaemia causing complete heart block was associated with concomitant administration of spironolactone and captopril in a 72-year-old woman (71). A similar reaction resulted in a patient taking spironolactone and enalapril (72). Hyperkalaemia in a further patient taking spironolactone and enalapril

<i>Combination</i>	<i>Interaction</i>
<b>Spironolactone/ACE inhibitor cont.</b>	persisted for over 48 hr despite discontinuation of the drugs and treatment with ion-exchange resins and i.v. glucose and insulin (73). This combination with ACE inhibitors is dangerous and should be avoided.
<b>Spironolactone/aspirin</b>	Administration of aspirin to healthy subjects taking spironolactone caused substantial reductions in Na <sup>+</sup> excretion (74) and the active metabolites (canrenone) excretion (75). However, administration of therapeutic doses of aspirin to hypertensive patients did not alter the effects of spironolactone on blood pressure, serum electrolytes, blood-urea nitrogen, or plasma renin activity (76).
<b>Spironolactone/digitoxin</b>	Spironolactone increased digitoxin half-life in normal subjects from 141.6 to 192.2 hr. This interaction may be harmful to digitoxin-intoxicated patients if they are treated with spironolactone for diuresis with K <sup>+</sup> -sparing effects. The combination should be used with caution (77).
<b>Spironolactone/digoxin</b>	Spironolactone and its metabolites have been reported to interfere with serum-digoxin determinations by radio-immunoassay or fluorescence-polarisation immunoassay resulting in falsely elevated measurements (78–81). This interference is neither consistent nor predictable and serum-digoxin concentrations should be interpreted with caution when the two drugs are given together, especially since spironolactone has also been reported to decrease digoxin clearance by a median of 26% resulting in a true increase in serum-digoxin concentrations (82).
<b>Spironolactone/mitotane</b>	Administration of the adrenocortical inhibitor, mitotane (up to 3 gm daily) to a patient with Cushing's syndrome appeared to be ineffective and did not produce the side effects usually associated with the drug when the patient was also given spironolactone (83). This combination should be avoided since it negates the effect of mitotane.
<b>Spironolactone/warfarin</b>	Spironolactone has been associated with a reduction in

<i>Combination</i>	<i>Interaction</i>
<b>Thiazide/ antihypertensive agent</b>	warfarin's activity in healthy subjects (84). It has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors (See also diuretic/anticoagulant entry above.)
<b>Thiazide/calcium carbonate</b>	Diuretics, particularly the thiazides, augment the hypotensive effects of antihypertensive drugs (85). This combination is common and valuable but the patient should be watched for excessive hypotension.
<b>Thiazide/cholestyramine, colestipol</b>	The milk-alkali syndrome (hypercalcaemia, metabolic acidosis, renal failure) developed in a patient taking chlorothiazide and moderately large doses of calcium carbonate (85). Patients taking thiazides may be at an increased risk of developing this syndrome due to their reduced ability to excrete excess calcium.
<b>Thiazide/digoxin</b>	Gastrointestinal absorption of both chlorothiazide and hydrochlorothiazide is reduced by cholestyramine and colestipol (86-88). In a study in healthy subjects, cholestyramine decreased hydrochlorothiazide absorption by 85%, compared with 45% decrease with colestipol (87).
<b>Thiazide/fenfluramine</b>	Hydrochlorothiazide and other thiazide diuretics may enhance the toxicity of digoxin and other digitalis glycosides by depleting serum-potassium concentrations (48, 49). This hypokalaemic effect may be enhanced by corticosteroids, corticotrophin, $\beta_2$ -agonists (salbutamol) or carbenoxolone (21, 89).
<b>Thiazide/lithium</b>	In nine of 43 obese patients hydrochlorothiazide did not lower blood pressure but raised the level of plasma noradrenaline (norepinephrine) in all patients with hypertension. Two to 5 weeks after adding fenfluramine to the thiazide in the nine obese and resistant patients, their blood pressures were reduced and there were marked falls in plasma noradrenaline concentrations (90). This may be a clinically useful interaction.
	Thiazide diuretics produce sodium depletion by

<i>Combination</i>	<i>Interaction</i>
<b>Thiazide/lithium cont.</b>	inhibiting distal tubular sodium reabsorption. The consequent increase in proximal tubular reabsorption frequently results in an increase in plasma lithium concentrations (22) with a risk of toxicity (24, 25). (See also entry on diuretic/lithium interactions above.)
<b>Thiazide/NSAID</b>	Interaction between thiazides or loop diuretics and NSAIDs may result in a reduction in the diuretic effect (91). Furosemide may not be effective in low birth weight infants receiving indomethacin (92), but furosemide can prevent the decline in urine output which occurs during indomethacin administration (93, 94).
<b>Thiazide/skeletal muscle relaxants</b>	Thiazides and ethacrynic acid increase the responsiveness to some skeletal muscle relaxants, an effect that seems to be related to induced K <sup>+</sup> deficiency (95–97). Avoid K <sup>+</sup> -depletion prior to elective surgery and if possible withhold the diuretic. Intensive preoperative electrolyte care is necessary to ensure that K <sup>+</sup> levels are normal (98).
<b>Thiazide/uricosuric drugs</b>	Thiazides frequently raise plasma levels of uric acid (99); the mechanism is uncertain. Thiazides may therefore disrupt the control of patients being treated for gout with uricosuric drugs. An increase in the uricosuric dosage (allopurinol, colchicine, probenecid, sulphapyrazone) may be necessary.
<b>Triamterene/ACE inhibitors</b>	As with other potassium-sparing diuretics there is a risk of hyperkalaemia if triamterene is taken in association with ACE inhibitors (100). They should not be given routinely with the diuretic.
<b>Triamterene/amantadine</b>	A patient with parkinsonism previously stabilized on amantadine (300 mg daily), showed amantadine toxicity symptoms (ataxia, myoclonus confusion) 7 days after starting treatment with triamterene and hydrochlorothiazide; it was thought that this was due to reduction of the tubular secretion of amantadine (101).

<i>Combination</i>	<i>Interaction</i>
<b>Triamterene/digoxin</b>	Triamterene in association with a thiazide or loop diuretic increased the mean serum-digoxin concentration; this interaction is thought to be of little clinical importance except in patients with renal failure (102).
<b>Triamterene/lithium</b>	Triamterene and the thiazide diuretics reduce the excretion of lithium and may thus precipitate intoxication (100).
<b>Triamterene/NSAID</b>	There have been reports of renal failure in patients taking NSAIDs with triamterene (98, 103). Both types of drugs are nephrotoxic and in combination their effects are additive (104–106). It is thought that suppression of urinary prostaglandins by NSAIDs could potentiate the nephrotoxic effects of the diuretic (98). NSAIDs may also antagonize the diuretic effect of triamterene (91).
<b>Triamterene/quinidine</b>	Triamterene may interfere with the fluorescent measurement of quinidine, and with some laboratory tests of thyroid and parathyroid function and with the bioassay of folic acid. Triamterene may cause a blue fluorescence of the urine under certain light conditions (100, 107).

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# **CHAPTER 3**

**Drug Interactions with Agents Used in  
Respiratory Disease**

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## **3.1. INTERACTIONS WITH SYMPATHOMIMETIC AMINES**

### **I. SYMPATHETIC AMINES USED IN THE TREATMENT OF ASTHMA**

#### **1. Selective $\beta_2$ -Adrenoceptor Stimulants**

**Salbutamol:** available in oral, injection and inhalation formulations

**Terbutaline:** available in oral, injection and inhalation formulations

**Bambuterol:** bambuterol is a prodrug of terbutaline and is available as an oral formulation

**Fenoterol hydrobromide:** available as inhalation formulations only

**Pirbuterol:** available as oral and inhalation formulations

**Reprotoberol:** available as inhalation formulation only

**Rimiterol hydrobromide:** available as inhalation formulation only

**Salmeterol:** salmeterol is an exceedingly long acting selective  $\beta_2$ -stimulant. It is not intended for immediate relief of acute bronchoconstriction. It is intended for patients needing long-term bronchodilator therapy. Adequate levels of inhaled corticosteroids will normally be co-prescribed. Salmeterol is available as a pressurized aerosol and a dry powder for inhalation.

**Tulobuterol:** available as oral preparations only

#### *Side effects of selective $\beta_2$ -stimulants*

Fine tremor, nervous tension, headache, palpitations, hypokalaemia, paradoxical bronchospasm, urticaria and angioneurotic oedema.

#### **2. Other Non-selective Adrenoceptor Stimulants Used for Treatment of Bronchoconstriction**

**Adrenaline hydrochloride and acid tartrate:** injections

**Ephedrine hydrochloride and sulphate:** oral formulations only

**Isoetharine hydrochloride:** available as oral formulations

**Isoprenaline hydrochloride and sulphate:** available as inhalation formulations only

**Orciprenaline sulphate:** available in oral and inhalation formulations

These preparations are now regarded as less suitable and less safe for use as bronchodilators than selective  $\beta_2$ -adrenergic stimulants as they are more likely to

cause cardiac arrhythmias and other side effects. They should be avoided whenever possible (BNF, 1995).

## **II. NON-SELECTIVE ADRENOCEPTOR STIMULANTS USED IN CONDITIONS OTHER THAN BRONCHOCONSTRICITION**

### **1. Cardiotropic Uses of Sympathomimetic Amine**

**Adrenaline and its salts**

**Isoprenaline and its salts**

**Dopamine**

**Dopexamine**

### **2. Nasal Decongestants**

**Ephedrine and its salts**

**Hydroxyamphetamine hydrobromide**

**Methoxamine hydrochloride**

**Naphazoline hydrochloride and nitrate**

**Oxymetazoline hydrochloride**

**Phenylephrine hydrochloride**

**Phenylpropanolamine hydrochloride**

**Pseudoephedrine hydrochloride**

**Tetrahydrazoline hydrochloride**

**Xylometazoline hydrochloride**

### **3. Hypertensive Agent**

**Angiotensin amide**

**Mephentermine sulphate**

**Metaraminol tartrate**

**Methoxamine hydrochloride**

**Noradrenaline acid tartrate**

**Oxedrine tartrate**

### **4. Uterine Relaxation**

**Isoxsuprime hydrochloride**

**Ritodrine hydrochloride**

Both these preparations are used as uterine muscle relaxants in the treatment of premature labour and are  $\beta$ -sympathomimetic agents.

**5. Ophthalmic Preparations****Adrenaline hydrochloride****Phenylephrine hydrochloride****6. Sympathomimetic Amines that have been Used for Weight Reduction****Amphetamine****Dexamphetamine****Diethyl propion****Fenfluramine****Dexfenfluramine****Phenylpropanolamine hydrochloride****Phentermine****7. Drugs of Abuse****Ecstasy:** an amphetamine derivative

These centrally acting appetite suppressants are of no real value in the treatment of obesity. They are all sympathomimetic amines and, with the exception of fenfluramine and dexfenfluramine, have pronounced stimulant effects on the central nervous system. Benefits are outweighed by the risks, and abuse is a continuing problem.

**GENERAL COMMENTS****Interaction with Antidepressants**

All sympathomimetic amines are contraindicated in patients receiving MAOI or tricyclic antidepressants.

**Sudden Death in Asthma**

Excessive use of aerosols containing sympathomimetic amines has been associated with sudden death in asthmatic, particularly young asthmatic, patients. This is thought to be due to the fact that some asthmatics become refractory to the actions of sympathomimetic amines as their condition deteriorates. In these circumstances cardiac effects of the sympathomimetic amines and the CFC propellants are accentuated in the presence of hypoxia (1).

The problem of inhalation toxicity studies on both drug and propellant therefore became pertinent since it was no longer possible to regard the propellants as being inert; they were fully capable of sensitizing the myocardium to some, but not all, sympathomimetic amines.

A study by Aviado and Belej (2) tested 15 different propellants used most widely and classified them into three groups:

*Class I:* Propellants that induced arrhythmia when given alone and also sensitized the heart to adrenaline-induced arrhythmia. This group includes trichlorofluoromethane (propellant 11), trichlorotrifluoromethane (propellant 113), (propellant 21), vinyl chloride, methylene chloride and trichloroethane.

*Class II:* Propellants that had no effect alone but sensitized the heart to adrenaline-induced arrhythmia, and this group includes propane, isobutane, dichlorotetrafluromethane (propellant 114), octafluorocyclohexane (propellant 12).

*Class III:* Propellants that neither caused arrhythmia nor sensitized the heart to adrenaline-induced arrhythmia. This group includes monochlorodifluoroethane (propellant 142b) and dichlorodifluoromethane (propellant 12).

Fluorocarbon 11, which was the most cardiotoxic in this study on the mouse heart, causing second- or third-degree heart block at 10% v/v, is also the most common propellant in pressurized aerosols used in asthma. (The cardiotoxic effect of propellant 11 could not be blocked by atropine, propranolol or sotalol showing that the effect is mediated by neither cholinergic nor  $\beta$ -adrenergic receptors.)

The potential interaction between sympathomimetic amines and CFC (Freon propellants) will be obviated by the reformulation for environmental reasons of pressurized aerosol formulations to eliminate CFC.

It is now believed that sudden asthma deaths are predominantly a result of underusage of steroids rather than overuse of sympathomimetic amines. In severe asthmatics regularly inhaled steroids should be routine, with or without a sustained release formulation of theophylline. Sympathomimetic amines used should be short acting selective  $\beta_2$ -stimulants and these should be used as rescue treatment for an acute episode of bronchoconstriction against a background of continuous inhaled and/or oral steroid therapy depending on the severity of the asthma.

### Urinary Retention in the Elderly

Sympathomimetic agents, particularly the non-selective agents may cause urinary retention in elderly males. This is largely due to  $\alpha$ -adrenergic effects. (Selective  $\alpha$ -adrenergic blockers, alfuzosin, indoramin, prazosin and terazosin, relax smooth muscle in the neck of the bladder in benign prostatic hyperplasia producing an increased flow and an improvement in obstructive symptoms).

<i>Combination</i>	<i>Interaction</i>
<b>Anaesthetics/adrenaline, isoprenaline (3, 4)</b>	A risk of arrhythmias exists if adrenaline or isoprenaline is given with volatile anaesthetics.

### ANTIDEPRESSANTS/SYMPATHOMIMETIC AMINES

**MAOI/dopamine (5)** Patients who have been treated with MAOI prior to

<i>Combination</i>	<i>Interaction</i>
	administration of dopamine should receive substantially reduced dosage of dopamine. The starting dose in such patients should be reduced to one tenth (1/10) of the usual dose.
<b>MAOI/dopexamine (6)</b>	Dopexamine is contraindicated in patients receiving MAOI
<b>MAOI/noradrenaline (7, 8)</b>	This interaction may produce a hypertensive crisis. However, noradrenaline is very rapidly taken up from circulation by adrenergic nerves and is inactivated by COMT enzyme. Therefore since monamine oxidase is probably little involved in this metabolism, the interaction is less likely than with other sympathomimetic amines which rely upon monoamine oxidase for their inactivation.
	Although noradrenaline is less likely to induce a hypertensive episode in patients receiving MAOI antidepressants than other sympathomimetic drugs, the risk is still present. Thus it would be wise to adhere to the general contraindication of all sympathomimetics in patients receiving such antidepressants.
<b>MAOI/ phenylpropanolamine (9-12)</b>	Hypertensive crises with fatal episodes have been reported with this interaction. Phenylpropanolamine is a common ingredient of many proprietary remedies designed to alleviate symptoms of the common cold, hay fever and rhinitis, etc.
	This combination is dangerous; phenylpropanolamine should not be given to patients being treated with a MAOI antidepressant or within 2 weeks of stopping such treatment.
	The UK government has (January 1984) proposed that all medicinal products containing phenylpropanolamine will be available <i>only on prescription</i> except where products are indicated for the relief of cough, colds and hay fever, with a recommended maximum daily dose of not more than 75 mg. The maximum permitted strength of nasal sprays and nasal drops will remain at

<i>Combination</i>	<i>Interaction</i>
<b>MAOI/ phenylpropanolamine <i>cont.</i></b>	2.0%. Phenylpropanolamine-containing slimming aids are still available, however, with little restriction in America and Australia.
<b>MAOI/phenylephrine (13)</b>	This combination may give rise to severe hypertensive crises. Phenylephrine is a common ingredient of many proprietary remedies (including non-prescription items) designed to alleviate symptoms of the common cold, hay fever, rhinitis etc.
	This combination is potentially dangerous and patients on MAOI treatment for depression should be warned of the dangers of using proprietary 'cold cures', nasal drops, etc. Patients should seek medical or pharmaceutical advice before such self-medication is commenced to ensure that phenylephrine or other sympathomimetic is absent from the formulation.
<b>MAOI/ sympathomimetic agents used in the treatment of obesity (3)</b>	MAOIs used in combination of the following sympathomimetic agents used in the treatment of obesity has resulted in hypertensive crises: amphetamine dexamphetamine dexfenfluramine diethyl propion fenfluramine phentermine phenylpropanolamine
<b>MAOI/ sympathomimetic amines used in nasal decongestants (3)</b>	All the list of sympathomimetic amines used in nasal decongestants can cause hypertensive crises when given to patients on MAOI inhibitors.
<b>Tricyclic antidepressants/ sympathomimetic amines (13–19)</b>	These antidepressants inhibit the uptake of noradrenaline by sympathetic neurones and this mechanism may be responsible for the increased cardiovascular actions of noradrenaline and the potentiation of noradrenaline toxicity.

<i>Combination</i>	<i>Interaction</i>
<b>Tricyclic antidepressant/isoprenaline (14)</b>	This type of combination is absolutely contraindicated, as is the concomitant use of tricyclic compounds with adrenaline or any other sympathomimetic amine.
	Imipramine potentiates the action of isoprenaline. The administration of imipramine (25 mg tid) to 10 chronic asthmatic patients using isoprenaline aerosols gave subjective improvement and increased peak expiratory flow. Cardiovascular responses to isoprenaline were also potentiated.
	Although the bronchodilator action of isoprenaline was enhanced, its cardiovascular effects were also potentiated, and could be potentially hazardous since tricyclic agents themselves cause cardiac arrhythmias. Patients on such a combination of treatments should be carefully observed for cardiovascular effects such as tachycardia and arrhythmias.
<b>Tricyclic antidepressants/local anaesthetics containing noradrenaline (7, 8, 18, 31)</b>	Fifteen cases of hypertensive episodes, one fatal, have been reported (32) in which local anaesthetic preparations containing high doses of noradrenaline (1 in 25 000 = 0.00004 g/ml) were used in dental anaesthesia. Six of these patients had been concurrently receiving treatment with tricyclic antidepressants (imipramine, desipramine, nortriptyline or protriptyline).
	The use of local anaesthetic formulations containing either of these vasoconstrictor agents is best avoided in patients on tricyclic antidepressants.
<b>Corticosteroids/selective <math>\beta_2</math>-sympathomimetic amines (32)</b>	There is a risk of hypokalaemia if high doses of corticosteroids are given with high doses of any of the following: bambuterol fenoterol pirbuterol reproterol rimiterol ritodrine salbutamol salmeterol

<i>Combination</i>	<i>Interaction</i>
<b>Corticosteroids/ Selective <math>\beta_2</math>-sympathomimetic amines cont.</b>	terbutaline tulobuterol Plasma potassium levels should be routinely monitored in severe asthmatics.
<b>Diuretics/selective <math>\beta_2</math>-sympathomimetic amines (32)</b>	There is a risk of enhanced hypokalaemia if high doses of bambuterol fenoterol pirbuterol reproterol rimiterol ritodrine salbutamol salmeterol terbutaline tolbutaline tulobuterol are given to patients on diuretics which are not potassium sparing. Plasma potassium levels should be routinely monitored in severe asthmatics.
<b>Ergot alkaloids/ sympathomimetic amines (33)</b>	The vasoconstrictor effects of ergot are enhanced, by sympathomimetic agents. Ergotamine has marked direct vasoconstrictor effects. The hydrogenation of alkaloids (e.g. dihydroergotamine and co-dergocrine (dihydro-ergotoxine) enhances their $\alpha$ -adrenergic blocking activity and diminishes their direct vasoconstrictor effects; thus these hydrogenated alkaloids will block the $\alpha$ -adrenergic effect of sympathomimetics.  This type of combination should only be used with caution and with full knowledge of the pharmacological nature of the interaction which, dependent upon the alkaloid, can vary from enhanced through diminished to reversed vasoconstrictor effects.  Ergometrine has been used as a provocation test for the variant of angina known as Prinzmetal's angina. In patients with Prinzmetal's angina the classic response

<i>Combination</i>	<i>Interaction</i>
	<p>consists of coronary arterial spasm accompanied by ST segment elevation on the ECG. Dose-related nausea, chest pain, and arrhythmias may occur and fatalities have been reported.</p>
	<p>Fatalities are more common in the presence of raised levels of endogenous sympathomimetic amines or exogenous sympathomimetic amines.</p>
<b>Insulin/ sympathomimetic amines</b> e.g. ritodrine (33)	Ritodrine given by i.v. infusion to an insulin-dependent diabetic to delay contractions in preterm labour caused hyperglycaemia (21.5 mmol/l) and ketoacidosis. She delivered a stillborn baby.
	<p>Avoid this combination; as diabetics do not have an adequate insulin response to handle <math>\beta</math>-adrenergic-induced hyperglycaemia, metabolic acidosis may occur and this could lead to fetal death.</p>
<b>Ipratropium/salbutamol (29)</b>	Shah <i>et al.</i> (29) have reported five cases of patients (aged 68–75 years) who developed acute angle closure glaucoma when they received both ipratropium and salbutamol as bronchodilators. The times between starting the nebulized therapy and the onset of symptoms ranged from 1 hr to an extreme of 9 days. The anticholinergic action of ipratropium caused pupil dilatation which blocked the flow of aqueous humour from the posterior to the anterior chamber of the eye which resulted in the peripheral iris bowing anteriorly and obstructing the drainage angle. Salbutamol compounded this problem by increasing the production of aqueous humour.
<b>Theophylline/selective <math>\beta_2</math>-sympathomimetic amines (30, 32)</b>	<p>There is an increased risk of hypokalaemia if theophylline is given with high doses of any of the following:</p> <ul style="list-style-type: none"> <li>bambuterol</li> <li>fenoterol</li> <li>pirbuterol</li> <li>reproterol</li> <li>rimiterol</li> <li>ritodrine</li> </ul>

<i>Combination</i>	<i>Interaction</i>
<b>Theophylline/selective <math>\beta_2</math>-sympathomimetic amines cont.</b>	salbutamol salmeterol terbutaline tulobuterol  Plasma potassium levels should be routinely monitored in severe asthmatics.
<b><math>\alpha</math>-Adrenergic blocking agents/sympathomimetic amine bronchodilators</b> (35, 36)	Indoramin and thymoxamine $\alpha$ -adrenergic blocking agents potentiate the bronchodilator effects of sympathomimetic amines.

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## **3.2. INTERACTIONS WITH THEOPHYLLINE AND DERIVATIVES**

**Theophylline hydrate**

**Theophylline monoethanolamine**

**Theophylline sodium glycinate**

**Acepifylline**

**Aminophylline**

**Choline theophyllinate**

**Diprophylline**

**Etofylline**

Since its recognition as a bronchodilator almost 50 years ago, theophylline, a methylxanthine alkaloid, has become a cornerstone in the management of both the acute and chronic phases of reversible airway obstruction. The drug also has proven efficacy in the management of apnoea in preterm infants. The drug, however, has a narrow therapeutic range that, along with its variability in disposition, makes dosing difficult to predict and toxicity difficult to prevent. Because of its narrow therapeutic range (10–20 µg/ml), theophylline is potentially fatal in children and adults if not administered with proper dose titration guided by plasma theophylline measurements. Symptoms of toxicity include tachycardia, severe restlessness, agitation, vomiting, headache and convulsions. The physical status of the patient can greatly alter theophylline metabolism and/or elimination, resulting in toxic plasma levels. After single doses of theophylline, significant decreases in plasma clearance and prolongation of plasma elimination half-life have been observed in patients with liver disease (acute hepatitis, cholestasis, cirrhosis) and acute pulmonary oedema/congestive heart failure.

Due to its narrow therapeutic range, theophylline is particularly prone to clinically significant interactions with other drugs.

Aminophylline is a mixture of theophylline and ethylenediamine which releases the active drug in the body; it can be regarded as a soluble derivative of theophylline; 1.27 g of aminophylline is approximately equivalent in theophylline content to 1 g of theophylline. Acepifylline (piperazine theophylline ethanoate), diprophylline (diphylline, dihydroxypropyltheophylline) and etofylline (hydroxyethyltheophylline) are also soluble derivatives of theophylline. All these derivatives have the actions and uses of theophylline.

Although theophylline has been used as a bronchodilator for more than 50 years, recent studies have indicated that theophylline has an anti-inflammatory action

which emerges at serum concentrations below those required to produce bronchodilation, and also below the levels associated with adverse effects such as arrhythmias, tachycardia, palpitations, nausea, gastrointestinal disturbance, headache, sleep disturbances, convulsions, etc. If low doses of theophylline are used then the tedious business of monitoring plasma levels, particularly for those in primary care can be avoided. The new role for theophylline may be regarded as steroid sparing.

Theophylline in this new role may become a first line anti-inflammatory therapy in asthma alongside steroids and cromoglycate.

### **Theophylline Modified Release**

The Council of the Royal Pharmaceutical Society of Great Britain advises pharmacists that if a general practitioner prescribes a modified release theophylline without specifying a particular formulation, the doctor should be contacted and a formulation decided upon.

Patients should be maintained on the same brand on which they have been stabilized.

### **Allergy to Ethylenediamine**

Allergy to ethylenediamine can cause urticaria, erythema and exfoliative dermatitis, and even fatal anaphylaxis.

<i>Combination</i>	<i>Interaction</i>
<b>Anaesthetics/theophylline</b>	
<b>Halothane (1, 2)</b>	Increased risk of cardiac arrhythmias when halothane is given to patients on theophylline.
<b>Ketamine (3)</b>	Extensor-type seizures have been described in four patients receiving theophylline after induction of anaesthesia with ketamine. It is suggested that anticonvulsant premedication be given to patients receiving theophylline or, alternatively, that ketamine be avoided in these patients.
<b>Anthelmintics/ theophylline</b>	
<b>Thiabendazole (1, 4-8)</b>	Thiabendazole increases theophylline concentration due to reduced hepatic metabolism of theophylline. It has been recommended that theophylline dosage should be reduced by 50% when thiabendazole therapy is started.

<i>Combination</i>	<i>Interaction</i>
<b>Anthelmintics/ aminophylline (7)</b>	Treatment of a patient on aminophylline infusion with thiabendazole for <i>Strongyloides</i> infection caused serum levels of theophylline to rise from 21 to 46 µg/ml. The likely mechanism of this interaction is inhibition of the liver metabolism of theophylline.
<b>Anti-arrhythmics/ theophylline</b> <b>Amiodarone (9)</b> <b>Mexiletine (1, 10–15)</b> <b>Propafenone (16)</b> <b>Tocainide (17)</b>	Amiodarone, mexiletine, propafenone and tocainide increase plasma theophylline concentration and may produce symptoms of theophylline toxicity (tachydardia, nervousness, tremors).
<b>Antibacterials/ theophylline</b> <b>Clarithromycin (1, 4–6)</b>	Plasma theophylline concentrations are increased by clarithromycin.
<b>Erythromycin (4, 18–28)</b>	<p>The effect of erythromycin on theophylline kinetics is controversial. Three studies in normal subjects have found no significant interaction between oral erythromycin and theophylline (18–20). However, one study in asthmatic children (21), one study in an adult patient with obstructive lung disease (22), and five studies in normal subjects (23–27) have shown that an interaction does occur and that erythromycin interferes with the disposition of theophylline, although the magnitude of the interaction is variable.</p> <p>In view of this divergence of opinion, and the absence of controlled studies on patients with chronic obstructive pulmonary disease and/or cor pulmonale, it would be prudent to assume that an interaction might occur. Precautions should therefore be taken to keep theophylline serum concentrations at the lower end of the therapeutic range (i.e. 8–115 µg/ml), and to monitor the patient for clinical signs of toxicity. Reliance can then be placed on bronchodilator combinations when more vigorous bronchodilation is required (28).</p>
<b>Isoniazid (29–31)</b>	Oral dosage of isoniazid (300 mg) for six consecutive nights increased mean oral theophylline clearance by

*Combination**Interaction***Isoniazid cont.**

16% in four healthy, non-smoking, male subjects. No consistent differences were noted in maximal plasma concentration, time of maximal plasma concentration, elimination half-life, absorption rate constant, elimination rate constant, area under the curve, or apparent volume of distribution. Although isoniazid is a well-documented inhibitor of the metabolism of many drugs, its effect on theophylline in this study appeared to be one of increased metabolism by either enzyme induction or an unknown mechanism (29).

More recent studies have shown that isoniazid inhibits oxidative enzymes in the liver and has been found to impair the elimination of theophylline. Both clearance and volume of distribution of theophylline were reduced with an increase in serum theophylline concentrations in healthy subjects after 14 days' pretreatment with isoniazid (30), and theophylline toxicity has been reported in a patient 1 month after adding theophylline to isoniazid therapy (31).

**Penicillins**

e.g. amoxycillin (51)

This combination is frequently prescribed. A study of the effect of amoxycillin (750 mg tds) on the pharmacokinetics of theophylline showed no effect.

**Quinolones**

e.g.  
ciprofloxacin  
enoxacin  
nalidixic acid  
norfloxacin  
perfloxacine  
pipemidic acid  
(1, 4-6, 32-50)

The fluoroquinolone antibiotics vary in their ability to interact with theophylline. The mechanism of interaction involves a reduction in the metabolic clearance of theophylline due to inhibition of hepatic microsomal enzymes. Enoxacin shows the strongest interaction and has been reported to cause serious nausea and vomiting, tachycardia and headaches associated with unexpectedly high plasma theophylline concentrations (32). Studies mainly in healthy subjects have found that enoxacin decreases theophylline clearance by up to 74% with an increase in the elimination half-life and plasma theophylline concentration (33-36). It has been recommended that the theophylline dosage be halved when enoxacin is started and that plasma theophylline levels be monitored.

<i>Combination</i>	<i>Interaction</i>
<b>Rifampicin</b> (1, 4, 30, 31, 52–56)	Ciprofloxacin (33, 37–39) and perfoxacin (33) interact with theophylline to a lesser extent than enoxacin, decreasing theophylline clearance by about 30%. Eight clinically important interactions between ciprofloxacin and theophylline have been reported by the Committee on Safety of Medicines, including one death, and it is recommended that ciprofloxacin should not be used in patients treated with theophylline (40). A ciprofloxacin-induced seizure has been reported which may have been due to the combined inhibitory effect of the two drugs on GABA binding (41). Norfloxacin (35, 42–44) and floxacin (35, 42, 45) have been reported to have minor effects on the pharmacokinetics of theophylline, although the American FDA has received reports of theophylline toxicity associated with concomitant norfloxacin administration including one death (46). Fleroxacin (47) and lomefloxacin (39, 48) appear to have no significant effect on the pharmacokinetics of theophylline, but cinafloxacin has been reported to increase theophylline serum concentration in an elderly patient (50). Of the non-fluorinated quinolones, nalidixic acid does not affect theophylline clearance (33), while pipemidic acid markedly inhibits theophylline clearance (49).
<b>Tetracyclines</b> (57–59)	Plasma theophylline concentrations are reduced by rifampicin due to increased hepatic clearance of theophylline. This interaction is sufficient to cause loss of clinical effect in some patients.
<b>Troleandomycin</b> (60)	Tetracycline weakly inhibits theophylline clearance; it has been reported to cause theophylline toxicity in one patient. Doxycycline has no significant effect on theophylline pharmacokinetics in health subjects.
	The macrolide antibiotic, troleandomycin, has been associated with decreased theophylline clearance. Clearance was decreased by 50% in eight patients who received troleandomycin (250 mg quid for at least 10 days). Serum concentrations of theophylline doubled in one patient. The mechanism of this interaction is likely

<i>Combination</i>	<i>Interaction</i>
<b>Troleandomycin cont.</b>	<p>to be a decreased hepatic uptake or altered enzymatic degradation in the liver.</p> <p>Caution is needed if these two drugs are to be used in combination. Reduction in theophylline dosage during the period of antibiotic administration may be required. The patient should be monitored for signs of theophylline toxicity.</p> <p>Troleandomycin has been reported to cause jaundice.</p>
<b>Anti-depressants/ theophylline</b> <b>Selective serotonin re-uptake inhibitors</b> <b>Fluvoxamine (1, 4, 19, 62, 63, 65–70)</b> <b>Viloxazine (1, 64, 65)</b>	<p>Plasma theophylline concentrations are increased by the SSRI antidepressants fluvoxamine and viloxazine. This is due to reduced hepatic metabolism of theophylline. Fluvoxamine is a potent inhibitor of the P450 isoform CYP1A2 (63). Theophylline toxicity due to this interaction has been reported.</p>
<b>Antiepileptics/ theophylline</b> <b>Carbamazepine (1, 4–6, 81)</b> <b>Phenobarbitone (1, 71–75)</b> <b>Primidone</b>	<p>These antiepileptic agents all increase hepatic clearance of theophylline due to enzyme P450 induction. (All barbiturates increase the rate of hepatic breakdown of theophylline due to enzyme induction.)</p>
<b>Phenytoin (76–81)</b>	<p>Pharmacokinetic studies in an asthmatic patient and in normal subjects showed that doses of phenytoin that gave plasma concentrations in the therapeutic range decreased the half-life of theophylline (mean 10.1–5.2 hr) and increased its clearance approximately two-fold. Phenytoin-induced hepatic enzyme induction is the likely mechanism of this interaction (79).</p> <p>It has also been shown in normal subjects that concomitant administration of theophylline and phenytoin reduced the absorption of the phenytoin dosage. Phenytion area under the curve values were decreased by 21% (80).</p> <p>The combined administration of theophylline with</p>

<i>Combination</i>	<i>Interaction</i>
	phenytoin in patients previously stabilized on phenytoin could lead to poor seizure control.
<b>Antifungals/theophylline fluconazole (1, 82, 83)</b>	Plasma theophylline concentrations increased by fluconazole with increased risk of theophylline toxicity. In a placebo controlled trial of administration of fluconazole 200 mg for 14 days, theophylline clearance was reduced by 18% (82).
<b>BCG/theophylline (84–85)</b>	BCG has been shown to impair the capacity of the liver to eliminate theophylline. There is therefore a possibility of transient rise in theophylline levels following BCG.
<b><math>\beta</math>-Adrenergic blocking agents/theophylline (86– 91)</b>	Propranolol (40 mg orally every 6 hr) significantly decreased theophylline clearance by a mean of 37%. This effect was more marked in smokers, in whom the metabolism of theophylline may already be induced (87, 88).
	Metoprolol (50 mg orally every 6 hr), the more likely agent to be used in asthmatic patients because of its cardioselectivity, did not significantly decrease the clearance of theophylline. However, there did appear to be an effect in some smokers whose initial clearance was high (87). The less lipophilic $\beta$ -adrenergic blockers atenolol (90, 91) and nadolol (91) have no significant effect on the pharmacokinetics of theophylline.
	The mechanisms of these interactions are not clear but theophylline metabolism may, at least in part, depend on stimulation of $\beta_2$ -receptors, which would be blocked more completely by propranolol than metoprolol (87). This could be due to effects on first-pass hepatic metabolism due to altered splanchnic blood flow. Propranolol and other non-selective $\beta$ -adrenergic blockers should not be used in asthmatic subjects who require bronchodilation. However, a decreased dose of

<i>Combination</i>	<i>Interaction</i>
<b><math>\beta</math>-Adrenergic blocking agents/theophylline</b> <i>cont.</i>	theophylline may be required in patients who smoke if treatment with metoprolol is initiated (86).
<b>Calcium channel blockers/theophylline</b> (92–101)	<p>Verapamil has been reported to decrease the clearance of theophylline by a mean of 14% in healthy subjects (92) and, although this was not considered to be clinically significant, symptoms of theophylline toxicity associated with near doubling of the serum-theophylline concentrations occurred in a 76-year-old woman taking theophylline after 6 days of therapy with verapamil (93).</p> <p>Studies in healthy subjects and asthmatics have produced conflicting results on the effect of nifedipine on the pharmacokinetics of theophylline. Reduced clearance (92) and an increase in the volume of distribution (94, 95) of theophylline have been reported, and both decreased and increased (96) theophylline concentrations; theophylline toxicity has been reported (97, 98). However, most studies have concluded that the effects of nifedipine are unlikely to be of clinical importance. Diltiazem has been reported to cause an increase (96, 101) and felodipine a decrease (100) in serum theophylline concentration, neither of which were considered to be clinically significant.</p>
<b>Disulfiram/theophylline</b> (1, 102)	Disulfiram increases theophylline concentrations due to hepatic enzyme inhibition, and may cause theophylline toxicity. Avoid combination.
<b>Diuretics/theophylline</b> (4)	Risk of hypokalaemia can be potentiated when xanthines and diuretics are given concurrently.
<b>Interferons/theophylline</b> (1, 103–106)	Plasma-theophylline concentration is increased by interferon $\alpha$ .
<b>Lithium/theophylline</b> (1, 4, 107)	Theophylline increases the renal excretion of lithium leading to reduced plasma lithium levels and reduced control of manic depression.

<i>Combination</i>	<i>Interaction</i>
<b>Lomustine/theophylline</b> (108)	In one case, the combination of theophylline and lomustine accelerated the leukopenia and thrombocytopenia common with this nitrosourea agent. Theophylline-induced phosphodiesterase inhibition in platelets increases intracellular cyclic AMP levels and may inhibit platelet function.  Oncologists should be alert to the possibility of augmented myelotoxicity and thrombopathia with this combination.
<b>Smoking/theophylline</b> (109–115)	Polycyclic hydrocarbons, such as those in cigarette smoke, are inducers of microsomal enzyme systems. It is established that cigarette smoking affects the disposition of theophylline, and that a patient's smoking status is an important consideration when selecting theophylline dosage (109–112). For example, theophylline clearance was significantly greater by 66% in smokers (0.0531 hr/kg) than in non-smokers (0.0321 hr/kg); clearance of theophylline metabolite was higher in smokers than in control subjects by almost two-fold (113). Results suggest that cigarette smoking induces both of the cytochrome P450-mediated pathways of theophylline metabolism, although <i>N</i> -demethylation may be increased to a greater extent than 8-hydroxylation (113).  Cigarette smoking significantly enhances the elimination of theophylline and this may be one of the factors that produces interindividual variability in theophylline clearance (114–115). In theory, therefore, a sustained-release preparation of theophylline would be more appropriate for patients who smoke so as to avoid excessive fluctuation in theophylline concentrations in the blood. The best advice, however, to offer the patient on theophylline is to stop smoking.

*Combination**Interaction***Steroid hormones/theophylline hydrocortisone (116)**

Three patients (116) in status asthmaticus were given a standard loading dose, then a constant infusion of theophylline until stable theophylline concentrations were attained (10–20 µg/ml).

Hydrocortisone (500 mg i.v. bolus then 6 hr later, three times 2-hourly 200-mg doses) caused a rapid elevation of theophylline concentrations to between 40 and 50 mg/ml with theophylline toxicity in two of the patients. No change in serum theophylline concentrations was seen in another theophylline treated patient who received saline in place of hydrocortisone.

The mechanism of this interaction is uncertain but it is advisable that patients on combined treatment be monitored for signs of theophylline toxicity. When possible serum theophylline levels should be frequently determined, and the dosage of theophylline reduced as necessary.

**Sympathomimetic amines/theophylline (1, 4–6) and (117–126)**

There is an increased risk of hypokalaemia if theophylline is given with high doses of bambuterol, fenoterol, pирbutерол, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, terbutaline and tulobuterol. It is recommended that serum potassium levels are monitored in such situations.

$\beta_2$ -Stimulant drugs increase cAMP production while theophylline inhibits its breakdown, giving rise to potential additive bronchodilator effects. However, an ephedrine–theophylline combination may increase toxicity without significantly increasing efficacy (117, 118). Other studies in patients with mild to moderate asthma indicated that a combination of ephedrine and theophylline produced a greater bronchodilation than either drug alone and that the addition of hydroxyzine gave further improvement (119–120).

Orciprenaline (metaproterenol) increases theophylline's effectiveness without increasing side

*Combination**Interaction*

effects (121–123). Terbutaline also showed additive effects to those of theophylline (124). Pulmonary function was found to improve significantly after inhalation of salbutamol (albuterol) after the maximum bronchodilator effect from theophylline had been achieved, or when the theophylline serum concentration reached 20 µg/ml without maximum effect (125, 126).

It appears that combination use of  $\beta_2$ -stimulants and theophylline may be useful if: (i) maximal bronchodilation cannot be achieved with appropriate doses of either agent alone; (ii) certain patients do not tolerate appropriate doses of either agent alone; or (iii) facilities are not available to monitor or interpret serum theophylline concentrations.

**Ulcer healing agents/theophylline (127–154)**

Increases in up to 25% in peak serum theophylline concentrations have been reported after concomitant oral administration of antacids (127, 128) although the oral absorption of theophylline does not seem to be affected (127, 129–130).

Comparative studies have suggested that ranitidine does not significantly inhibit theophylline metabolism (131–136) even at very high dosage (135), although there have been occasional reports of theophylline toxicity after concomitant ranitidine therapy (136–138). Famotidine does not alter theophylline disposition (139), but etinidine reduced the clearance of theophylline and prolonged its elimination half-life (140).

In contrast, cimetidine (1 g/day for 7 days) induced a 35% fall in systemic clearance of theophylline under the same conditions (e.g. 30 min i.v. infusion of theophylline (154)).

An early report indicated that the elimination half-life of theophylline was increased by a mean of 60% after cimetidine administration (141). More detailed studies

<i>Combination</i>	<i>Interaction</i>
<p><b>Ulcer healing agents/theophylline</b> <i>cont.</i></p>	<p>have shown that cimetidine significantly decreased theophylline clearance by a mean of 39%; the apparent volume of distribution was unchanged, whereas the elimination rate constant was significantly decreased by a mean of 42%. This corresponded to an average increase in elimination half-life of 73% (142). Other studies in young and elderly patients (143–147) and in healthy subjects (148, 149) have produced similar findings. The mechanism of this interaction is thought to be the inhibitory effect of cimetidine on hepatic microsomal mixed-function oxidases such as cytochrome P450 and P448 (142, 149, 150).</p> <p>Three cases have been reported in which cimetidine apparently reduced the rate of metabolism of aminophylline. The first of these (151), cimetidine (300 mg qid) in an elderly patient evoked a grand mal seizure; her EEG was consistent with a toxic or cerebral process. Large doses of aminophylline had been used before cimetidine was started without any complications. In the second case (152) theophylline clearance was 4.75 l/hr before and 1.17 l hr during cimetidine (300 mg qid) treatment and theophylline half-life increased from 2.7 to 7.8 hr. Steady-state theophylline levels rose from 4.2 µg/ml before cimetidine to 25.7 µg/ml during cimetidine treatment. The third case (152) had end-stage liver disease; her theophylline half-life was tremendously long (118.8 hr) and termination of cimetidine reduced this to 65.2 hr. During cimetidine dosage her serum theophylline concentration was 41.2 µg/ml. She died after liver failure. The rapid decrease in theophylline half-life in this patient and the fact that cimetidine is not extensively metabolized has suggested that cimetidine reversibly binds to the enzyme systems that metabolize theophylline without actually interfering with the intrinsic activity.</p> <p>It has been suggested that the cimetidine–theophylline interaction does not occur in the liver, and that theophylline forms a complex with cimetidine in the blood, thus preventing theophylline from being metabolized (153).</p>

<i>Combination</i>	<i>Interaction</i>
<b>Uricosurics/theophylline</b> <b>Allopurinol</b> (1, 4–6, 155–157)	<p>Allopurinol (300 mg every 12 hr for 14 or 28 days) inhibited the metabolism of theophylline in normal subjects. Half-life increased by 25% and AUC by 27%. Allopurinol given for 7 days under the same conditions did not affect theophylline's disposition (155). Two other studies also showed that pretreatment of normal subjects with oral allopurinol (300 mg daily) for short periods had no effect on the disposition of theophylline (156, 157). The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. Allopurinol, a hypoxanthine derivative, is a competitive inhibitor of xanthine oxidase. High-dose allopurinol (300 mg bd) is likely to increase theophylline levels.</p> <p>The interaction is only likely to occur with relatively high doses (but still within the clinical range) of allopurinol given for periods longer than 7 days. The interaction could also occur at lower doses of allopurinol in patients whose theophylline elimination was already compromised. Use of this combined treatment may therefore require a reduction in theophylline dosage to avoid its accumulation and toxicity. Monitor theophylline levels in patients starting or increasing allopurinol.</p>
<b>Sulphinpyrazone</b> (1, 158)	Plasma-theophylline levels are reduced by sulphinpyrazone due to selective inhibition of cytochrome P450 enzymes.
<b>Vaccines/theophylline</b> (159–168)	<p>Eleven children whose asthma had been controlled with a stable theophylline dose developed signs of theophylline toxicity on the same dose during an influenza B outbreak (159). All had clinical evidence of a febrile viral illness. Two children had seizures, eight had nausea and vomiting, and three had headaches. Theophylline clearance gradually returned to pre-illness levels over a period of 1–3 months (159). These cases supported the earlier contention that theophylline clearance was decreased during natural viral respiratory infections (160–162).</p> <p>Decreased elimination of theophylline also occurred</p>

<i>Combination</i>	<i>Interaction</i>
<b>Vaccines/theophylline</b>	
<i>cont.</i>	
	after influenza immunization in patients and in volunteer subjects (161). In contrast, other studies have indicated that influenza immunization had no effect on theophylline levels in patients with chronic airway obstruction (163, 164). However, the original investigators have reiterated their previous conclusion that influenza vaccine <i>does</i> alter theophylline metabolism, and have suggested that the discrepancy in findings may be due to the use of different vaccines and that these may have different peak timing of their depressant effect on drug metabolism (165).
	Agents that induce interferon can inactivate hepatic cytochrome P450. In as much as viruses are inducers of interferon, this synthesis may be the most likely mechanism of influenza virus and vaccine in altering theophylline pharmacokinetics (166). Support is given to this by the demonstration that influenza vaccination depresses aminopyrine metabolism in man (167).
	More recently, a study in elderly subjects showed that clinically significant reactions to warfarin or theophylline were rare after influenza vaccinations, and were no more frequent than in those not receiving vaccinations. Further, following influenza vaccination in 13 elderly individuals serum concentrations of theophylline showed no change. Others have found no effect of influenza vaccine on theophylline clearance in normal subjects nor in those with chronic obstructive airways disease.
	It must also be appreciated that, in theophylline-treated patients, symptoms of vomiting, headaches or seizures during viral illness may be due to theophylline toxicity rather than to the virus. Such patients should have an immediate serum theophylline determination even if previous levels were in the therapeutic range (159).
	In practice clinically significant interactions have been shown to occur with influenza virus infections but not following vaccinations.
	The British National Formulary remains cautious by

*Combination**Interaction*

stating "plasma-theophylline concentrations occasionally increased by influenza vaccine". The Data sheets to none of the commercially available influenza vaccines refer to this interaction (168).

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## **3.3 ANTIHISTAMINES**

### **INTRODUCTION**

Histamine exerts its actions via two types of receptors. Actions such as the stimulation of smooth muscle of the intestine and bronchi are antagonized by the conventional antihistamines and H<sub>1</sub>-receptors are involved. Actions of histamine not antagonized by conventional antihistamines, for example stimulation of gastric juice, inhibition of uterine contractions and increase in heart rate, have been shown to involve H<sub>2</sub>-receptors. This present section will only deal with interactions involving H<sub>1</sub>-receptor antagonists. Interactions involving H<sub>2</sub>-receptor antagonists have already been detailed in Chapter 1 (agents used to treat gastrointestinal disease).

Many conventional antihistamines have other pharmacological properties largely independent of antihistaminic activity. These include anticholinergic, anti-adrenaline and antiserotonin effects. Some, including cinnarizine and flunarizine, have calcium channel blocking activity. Most antihistamines are also CNS depressants, although in very large doses they may cause CNS stimulation; most have some local anaesthetic properties. Side effects with antihistamines vary in incidence and severity with each patient as much as with each drug. The most common effects are sedation, varying from slight sedation to deep sleep, inability to concentrate, lassitude, dizziness, muscular weakness and incoordination. Sedative effects often diminish after a few days when tolerance is acquired.

Other side effects include nausea, vomiting, diarrhoea, colic and epigastric pain; antihistamines may also produce headache, blurred vision, tinnitus, irritability, anorexia and dry mouth. In infants and children, some antihistamines have cerebral stimulant properties, and overdosage may evoke convulsions and hyperpyrexia. CNS stimulation may arise in some adults, especially after phenindamine tartrate which differs from most conventional antihistamines in giving rise to stimulant side effects and not sedation. Large doses of antihistamines may precipitate fits in epileptics.

Antihistamines should be used with caution in epilepsy, prostatic hypertrophy, urinary retention, glaucoma and hepatic disease (especially astemizole and terfenadine) if there is significant impairment. Most antihistamines should be avoided in porphyria, but chlorpheniramine and cyclizine are thought to be safe. Some antihistamines have been associated with fetal abnormalities when taken during pregnancy, but a large number of studies have failed to demonstrate any strong associations; some packs of antihistamines sold to the public carry warnings to avoid

in pregnancy (1). The manufacturers of astemizole advise avoiding during pregnancy (2).

Significant amounts of some antihistamines occur in breast milk and, although not known to be harmful, some manufacturers advise avoiding antihistamines whilst breast-feeding (3). Drowsiness, irritability and refusal to feed has been reported in a 10-week-old breast-fed baby, 12 hr after her mother started treatment with clemastine (4).

There are undoubtedly too many antihistamines available; although they may be classified according to their chemical structures, this offers little useful information to the clinician. An attempt has therefore been made in this present context to divide the conventional antihistamines in common medicinal use into two groups: Group 1, non-sedative; and Group 2, sedative. The majority of conventional antihistamines fall into Group 2.

There is no evidence that any one of the older sedative antihistamines is superior to any other and patients vary widely in their responses. Acrivastine, astemizole, cetirizine, loratadine and terfenadine are newer antihistamines; they are a major advance over the older antihistamines. They cause less sedation and psychomotor impairment because they only penetrate the blood-brain barrier to a slight extent (and for this reason do not alleviate pruritus of non-allergic origin). Astemizole has a relatively slow onset on action and is more appropriate for use on a regular basis than when symptoms occur (1BNF, ch 3.4, p. 135).

#### **GROUP 1: NON-SEDATIVE\* ANTIHISTAMINES**

**acrivastine**  
**astemizole**  
**cetirizine**  
**loratadine**  
**terfenadine**

\*Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. driving): excess alcohol should be avoided.

#### **GROUP 2: SEDATIVE ANTIHISTAMINES**

<b>azatadine maleate</b>	<b>doxylamine</b>
<b>brompheniramine maleate</b>	<b>flunarizine hydrochloride</b>
<b>buclizine</b>	<b>hydroxyzine hydrochloride</b>
<b>chlorpheniramine maleate</b>	<b>ketotifen</b>
<b>cinnarizine</b>	<b>mequitazine</b>
<b>clemastine</b>	<b>phenindamine tartrate</b>
<b>cyclizine</b>	<b>pheniramine maleate</b>
<b>cyproheptadine hydrochloride</b>	<b>promethazine hydrochloride</b>

**dimenhydrinate**  
**diphenhydramine hydrochloride**  
**diphenylpyraline hydrochloride**

**promethazine theoclate**  
**trimeprazine tartrate**  
**triprolidine hydrochloride**

## INDICATIONS

Antihistamines are used for the symptomatic relief of hypersensitivity reactions; they are generally considered to be ineffective in asthma. Acute anaphylaxis should be treated with adrenaline; antihistamines and corticosteroids are given to prevent relapse. Antihistamines are used to control the pruritus associated with skin disorders; some including promethazine are used for their sedative effects. Some have anti-emetic properties and are used to control nausea and vomiting due to a number of causes, especially motion sickness. They are also used in the symptomatic treatment of the vertigo, nausea and vomiting of Ménières disease and other vestibular disorders. Buclizine and cyclizine are used to alleviate the nausea and vomiting associated with migraine; cyproheptadine and flunarizine may be of value in the prophylaxis of migraine in children. Antihistamines are widely used, often with a decongestant, in compound preparations for the symptomatic treatment of cough and the common cold; there is little evidence such preparations are effective.

Topical application of antihistamines is generally considered to be inadvisable because of the risk of skin sensitization reactions; dermatological reactions may occasionally occur after oral dosage.

## INTERACTIONS

Antihistamines are most likely to enhance the sedative effects of CNS depressants including alcohol, barbiturates, hypnotics, opioid narcotics, anxiolytics, sedatives, and neuroleptics. MAOI antidepressants may enhance the the antimuscarinic effects of antihistamines, and antihistamines have an additive effect with other antimuscarinic drugs such as atropine, tricyclic antidepressants and similar compounds.

It has been suggested that antihistamines could mask the warning signs of ototoxicity caused by the aminoglycoside antibiotics and other ototoxic agents. The potential for ventricular arrhythmias should be kept in mind when astemizole or terfenadine are used in combination with other drugs, especially since both these antihistaminics are available in the UK without prescription.

Antihistamines may suppress positive skin test results and should be stopped several days before these tests. It should be noted that some antihistamines are incompatible, *in vitro*, with other drugs if mixed in injections or infusions (5), a list of these incompatibilities, most of which are reported in early publications, is included at the end of the following Table of Drug Interactions.

<i>Combination</i>	<i>Interaction</i>
<b>Antihistamine/ anticholinesterase</b>	Some antihistamines have significant anticholinergic effects (e.g. cyclizine, cyproheptadine,

<i>Combination</i>	<i>Interaction</i>
<b>Antihistamine/ anticholinesterase <i>cont.</i></b>	diphenhydramine, phenindamine, promethazine, trimeprazine, etc); this will antagonize the miotic effect of an anticholinesterase drug. Such combinations should be avoided. (6).
<b>Antihistamine/ anticonvulsant carbamazepine</b>	A case has been reported on an interaction between terfenadine and the anticonvulsant carbamazepine. The patient, an 18-year-old woman, was on anticonvulsant therapy after treatment for brain metastases. She was admitted to hospital with symptoms of confusion, disorientation, visual hallucinations, nausea and ataxia and she had a history of atopia. These symptoms started shortly after taking terfenadine (60 mg twice daily by mouth) for symptomatic relief of rhinitis. Serum levels of carbamazepine were almost three times the normal level. Since both drugs are highly protein bound, the clinicians thought that the terfenadine had displaced the carbamazepine resulting in the increased serum levels. After stopping the terfenadine, symptoms resolved and serum levels of carbamazepine returned to within the normal range (7). These drugs should not be used concomitantly.
<b>phenytoin</b>	A young woman developed drowsiness, ataxia, diplopia, and tinnitus and episodes of occipital headache associated with vomiting after concomitant administration of phenytoin sodium and chlorpheniramine (8). Chlorpheniramine was thought to delay the hepatic metabolism of phenytoin and increase its plasma concentration to toxic levels.
<b>Antihistamine/ buphenine</b>	Antihistamines having a phenothiazine structure (e.g. mequitazine, trimeprazine, promethazine) are potentiated by the sympathomimetic vasodilator buphenine, which acts predominantly on $\beta$ -adrenergic receptors (9, 10). These drugs should not be used concurrently.
<b>Antihistamine/ Ca-channel blocker</b>	Cinnarizine is a calcium-channel blocker; the Spanish System of Pharmacovigilance has received reports of tinnitus associated with calcium-channel blockers, including one relating to cinnarizine, when patients

*Combination**Interaction*

also received other ototoxic drugs (11). WHO have additional reports of tinnitus associated with calcium-channel blockers including cinnarizine.

**Antihistamine/  
catecholamine**

Some, but not all, antihistamines potentiate the cardiovascular effects of adrenaline and noradrenaline. This is due to inhibition of neural uptake of catecholamine, resulting in an increased amount of unbound catecholamine which then reacts with cardiac and vascular receptor sites (12). The possibility of increased catecholamine toxicity should be realized. Since catecholamines are histamine antagonists, the need for concomitant antihistamine dosage is virtually minimal. Fixed combinations of antihistamines and catecholamines are therefore illogical.

**Antihistamine/  
chloroquine**

Cyproheptadine has been shown to reverse chloroquine resistance in malaria parasites *in vitro*. However, clinical studies have been disappointing as they have not shown this and other drugs (e.g. desipramine, verapamil to be effective at clinically tolerable dosage (13–17).

**Antihistamine/CNS  
depressant (6)**

Antihistamines are most likely to enhance the sedative effects of all CNS depressants including alcohol, barbiturates, hypnotics, opioid narcotics, anxiolytics, sedatives and neuroleptics. This type of interaction has been frequently documented and many deaths have resulted. In particular alcohol and other CNS depressants may so enhance the effects of antihistamines that patients are at special risk when driving or operating any machinery where loss of attention may lead to accidents.

**Antihistmine/  
diagnostic test  
cyproheptadine**

Cyproheptadine reduced hypoglycaemia-induced growth hormone secretion by between 5 and 97% in eight healthy subjects (18). It was suggested that if patients receiving cyproheptadine were given a pituitary function test which used growth hormone response to insulin-induced hypoglycaemia, then

<i>Combination</i>	<i>Interaction</i>
<b>Antihistmine/ diagnostic test cyproheptadine <i>cont.</i></b>	cyproheptidine treatment should be stopped before the test.
<b>diphenhydramine</b>	There has been a report suggesting that since diphenhydramine inhibits the cytochrome P450 enzyme system, it may interfere with the debrisoquine testing for genetic polymorphism (19).
<b>Antihistamine (astemizole)/ erythromycin ketoconazole itraconazole</b>	<p>The US Food and Drug Administration has warned that astemizole should not be prescribed in combination with the antifungal drugs, ketoconazole or itraconazole, or the antibiotic, erythromycin (20). The FDA have received reports of serious cardiac arrhythmias in two patients who took astemizole with erythromycin or with erythromycin plus ketoconazole. The FDA has also issued a similar warning for another antihistamine, terfenadine (21) (see below). Both antihistamines are metabolized in the liver and are potentiated in their effects (raised plasma concentrations) by drugs which are potent inhibitors of hepatic microsomal enzymes, notably erythromycin and ketoconazole. The FDA have included itraconazole in the warning because of its chemical and pharmacological similarity to ketoconazole. The UK Committee on Safety of Medicines has issued a similar warning and has cautioned that at high serum concentrations, or as a consequence of drug interaction, they prolong the QT interval and thus have the potential to induce ventricular arrhythmias. By October 1992, the CSM had received 18 reports of adverse reactions with astemizole affecting the cardiovascular system, and 94 reports (including three sudden deaths and three other fatalities) of similar adverse reactions to terfenadine.</p>
<b>Antihistamine/ anti-arrhythmics neuroleptics tricyclics diuretics</b>	The CSM cautioned against concomitant administration of astemizole or terfenadine with drugs having an arrhythmogenic potential such as anti-arrhythmics, neuroleptics, tricyclic antidepressants, diuretics and drugs producing an electrolyte imbalance. The CSM warned that astemizole or terfenadine

*Combination***fluvoxamine***Interaction*

should not be used in combination with erythromycin or oral ketoconazole. The CSM also suggested that it would also be prudent to avoid concomitant use of other macrolide antibiotics and imidazole antifungal agents (notably itraconazole) (22).

It has also been advised that use with fluvoxamine be avoided. Astemizole should not be used in patients with pre-existing prolongation of the QT interval or hypokalaemia or other electrolyte imbalance. Concomitant administration with potentially arrhythmogenic agents, such as anti-arrhythmic agents, tricyclic antidepressants, antipsychotics, sotalol, halofantrine, terfenadine, or diuretics that produce hypokalaemia should be avoided (23). The toxic potential of astemizole or terfenadine (see below) either alone or each in combination with interacting drugs is a matter of concern; they are widely used for the treatment of hay fever and allergic conditions and in the UK are available from pharmacies without prescription.

**Antihistamine  
(cyclizine)/  
methohexitone and  
narcotic analgesics**

Cyclizine lactate (50 mg) was a poor preoperative sedative. It increased the incidence of excitatory phenomena after methohexitone anaesthesia, enhanced the soporific effects of pethidine but reduced both preoperative and postoperative sickness (24). In later studies cyclizine was shown to reduce significantly the incidence of vomiting associated with oral dihydrocodeine, dipipanone, levorphanol, methadone, or pethidine (25). Cyclizine lactate is incompatible with morphine sulphate in solution (26).

**Antihistamine  
(diphenhydramine)/  
temazepam**

There is a report suggesting that a reduction in temazepam metabolism caused by diphenhydramine may have contributed to a perinatal death after ingestion of these drugs by the mother (10). This combination should be avoided especially by pregnant women. The manufacturers of temazepam warn that the drug should not be used during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.

<i>Combination</i>	<i>Interaction</i>
<b>Antihistamine (loratadine)/ erythromycin</b>	Data held on file by the manufacturers show that erythromycin can inhibit the metabolism of loratadine. However, even when given in large doses, loratadine does not appear to cause cardiac conductive disorders associated with other non-sedative antihistaminics such as astemizole and terfenadine (27). Ketoconazole appears to be able to inhibit the metabolism of loratadine and, at therapeutic doses, is apparently three times more inhibitory than erythromycin (28). However, the concentrations of ketoconazole required are reported to be much higher than those required to inhibit the metabolism of astemizole or terfenadine. Cimetidine also appears to inhibit the metabolism of loratadine and all three drugs also attenuate the clearance of its active metabolite descarboethoxy-loratadine although no clinically significant consequences were observed in these studies (28).
<b>ketoconazole</b>	
<b>cimetidine</b>	
<b>Antihistamine (terfenadine)/ erythromycin clarithromycin itraconazole ketoconazole troleandomycin</b>	Terfenadine is extensively metabolized in the liver and the toxicity of the parent compound is increased by inhibitors of hepatic metabolism (29). Pharmacokinetic studies have demonstrated that the macrolide antibiotics, erythromycin (30) and clarithromycin (31) and the imidazole antifungal agents, itraconazole (32) and ketoconazole (33) interfere with the metabolism of terfenadine leading to its accumulation. A high plasma terfenadine concentration is associated with prolongation of the QT interval and arrhythmias such as <i>torsade de pointes</i> have been reported in patients treated with therapeutic doses of terfenadine and erythromycin (34), troleandomycin (35), ketoconazole (36) or itraconazole (32, 37). Cardiac abnormalities have occurred in patients taking terfenadine and fluoxetine concomitantly (38). The manufacturers literature states that concomitant administration of terfenadine with erythromycin, clarithromycin, troleandomycin, itraconazole or ketoconazole is contraindicated. Some authorities also include other macrolide antibiotics and other imidazole antifungals in this contraindication. There has been a pharmacokinetic study that suggested that the interaction between terfenadine and fluconazole might
<b>fluoxetine</b>	
<b>fluconazole</b>	

*Combination**Interaction*

not be clinically significant as the mechanism of the interaction appeared to involve the metabolite of terfenadine and did not lead to the accumulation of the cardiotoxic parent compound (39). But this may not always be so, since studies in small groups of patients who exhibited abnormal patterns of terfenadine metabolism demonstrated increases in terfenadine concentrations associated with ECG abnormalities when terfenadine was given with high doses of fluconazole (40); the manufacturers warn against the use of this combination.

**Antihistamine/  
grapefruit juice**

A variety of drugs (see review (41)) including terfenadine interact with grapefruit juice and potentiate their effects (42). The mechanism of this interaction is inhibition of cytochrome P450 by the bitter flavonoids (naringin, naringenin, quercetin, kaempferol) present in grapefruit juice; terfenadine being metabolized by the family member CYP3A4. The most recent study on the effects of grapefruit juice on the pharmacokinetic and electrocardiographic repolarization pharmacodynamics of terfenadine in poor metabolizers of terfenadine showed an accumulation of unmetabolized parent compound and more importantly the changes in ECG repolarization that resulted from this accumulation (43). The results were consistent with a former study on subjects who were not poor metabolizers of terfenadine (42). The authors suggested that the prolongation of the QT interval caused by this interaction might cause an increased risk of arrhythmias especially for *torsade de pointes* patients. However, there are no reports in the FDA Spontaneous Reporting System database which implicates grapefruit juice as a co-factor in terfenadine-related morbidity or mortality. The authors of the report believe that it is unlikely that practitioners would have appreciated the effect of this popular beverage on drug pharmacokinetics. In the UK, the Medicines Control Agency is currently investigating the possible interaction between terfenadine and grapefruit juice which is reported to

<i>Combination</i>	<i>Interaction</i>
<b>Antihistamine/ grapefruit juice cont.</b>	more than double the plasma levels of the unchanged drug (44).
<b>Antihistamine (tripelennamine)/other antihistamines</b>	A severe toxic reaction including agitation, hallucinations and myoclonic jerks occurred in an 8-year-old child who was sprayed over the trunk and extremities with an aerosol of tripelennamine hydrochloride in the treatment of severe poison ivy poisoniong (45). It was likely that the inhalation of the fine aerosol spray was responsible for these reactions, but the original reaction was inadvertently prolonged by subsequent treatment with diphenhydramine and promethazine.
<b>Antihistamines/other drugs in solution</b>	Antihistamines have been frequently given intravenously with other drugs to diminish unwanted reactions to these other agents. This practice has given rise to a large number of physicochemical incompatibilities. Some data are presented here; regarding incompatibilities in solutions, they have been gained from the monographs of individual antihistamines in the latest edition of <i>Martindale, The Extra Pharmacopoeia</i> (46) and from the literature. Further information should be obtained from the manufacturers.
<b>Brompheniramine maleate</b>	Incompatible with some diatrizoate, iodipamide and iothalamate salts (47).
<b>Chlorpheniramine maleate</b>	Incompatible with calcium chloride, kanamycin sulphate, noradrenaline acid tartrate, pentobarbitone sodium and iodipamide meglumine (47, 48).
<b>Cyclizine lactate</b>	Injection incompatible with morphine sulphate (26), oxytetracycline hydrochloride, chlortetracycline hydrochloride, benzylpenicillin, and solutions with a pH of 6.8 or more.
<b>Dimenhydrinate</b>	Incompatible in solution with aminophylline, ammonium chloride, chloramphenicol, heparin, hydrocortisone sodium succinate, hydroxyzine hydrochloride, iodipamide, glycopyrronium bromide,

<i>Combination</i>	<i>Interaction</i>
	methoxamine, meglumine, nicotinic acid, some phenothiazines, phenytoin, prednisolone, promazine hydrochloride, promethazine hydrochloride, pyridoxine hydrochloride, radio-contrast media, some soluble barbiturates, and tetracycline (47–51).
<b>Diphenhydramine</b>	Incompatible with amphotericin, cephalothin sodium, hydrocortisone sodium succinate, some soluble barbiturates, some contrast media and solutions of alkalis or strong acids (48, 51–54).
<b>Hydroxyzine hydrochloride</b>	Incompatibility with aminophylline, benzylpenicillin salts, chloramphenicol sodium succinate, dimenhydrinate, thioridazine, and some soluble barbiturates. However, an aqueous mixture of hydroxyzine hydrochloride, chlorpromazine hydrochloride, and pethidine hydrochloride stored in glass or plastic syringes was stable for 1 year at room temperature (55).
<b>Promethazine hydrochloride</b>	Incompatible with alkaline substances which precipitate the insoluble base, aminophylline, barbiturates, benzylpenicillin salts, carbenicillin sodium, chloramphenical sodium succinate, chlorothiazide sodium, cefoperazone sodium, dextran, dimenhydrinate, diodone, ethamivan, frusemide, heparin sodium, hydrocortisone sodium succinate, methicillin sodium, morphine sulphate, nalbuphine hydrochloride, nitrofurantoin, phenytoin, prednisolone, some contrast media, sulphadimidine and sulphafurazole (47, 48, 51, 53, 56–58).
<b>Thiethylperazine maleate</b>	Incompatibility with nalbuphine hydrochloride injection (59).
<b>Tripelenamine hydrochloride</b>	Incompatible with the following drugs in solution: chloramphenicol sodium succinate, phenobarbitone sodium and phenytoin sodium (48).

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# **CHAPTER 4**

**Drug Interactions with Agents Used in  
the Treatment of CNS Disorders**

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## **4.1 INTERACTIONS WITH DRUGS USED IN THE TREATMENT OF SCHIZOPHRENIA AND RELATED PSYCHOSES**

Antipsychotic agents are also known as neuroleptics and as major tranquillisers although the latter term is misleading. Neuroleptics include the phenothiazines, butyrophenones and related compounds, and the thioxanthines. All are used in the treatment of psychoses such as schizophrenia, mania, senile dementia and certain behavioural disorders of children.

Rauwolfia alkaloids, notably reserpine were similarly used in these conditions but should now be regarded as obsolete. Antipsychotic drugs are considered to act by interfering with dopaminergic transmission in the brain by blocking dopamine receptors and thus may give rise to extrapyramidal side effects, including tardive dyskinesia, and also to hyperprolactinaemia and gynaecomastia due to inhibition of the release of prolactin-releasing inhibitory factor. Antipsychotic agents all have some  $\alpha$ -adrenergic, histaminergic and serotonergic antagonist/agonist effects.

### **I. PHENOTHIAZINES**

There are undoubtedly far too many phenothiazines available and, although they can be readily classified according to their chemical structure, this *per se* offers little useful information to the clinician. However, although the properties of the phenothiazines are similar, there are quantitative and qualitative differences in their action which can be relevant in their selection.

#### **Group 1: Phenothiazines with a Dimethyl-amino-propyl Side Chain**

Phenothiazines with the dimethyl-amino-propyl side chain generally have a marked sedative effect and are of value in the treatment of psychoses where agitation is a feature. This group of phenothiazines has moderate antimuscarinic effects and a moderate propensity to cause extrapyramidal side effects. Tardive dyskinesia can occur with prolonged administration.

**Chlorpromazine**

**Fluopromazine**

**Methotriimeprazine**

**Promazine****Prothipendyl hydrochloride****Group 2: Phenothiazines with a Piperidine Side Chain**

This group is characterized by fewer moderate sedative effects, marked antimuscarinic effects and fewer extrapyramidal effects than Groups 1 and 3.

**Pericyazine****Piperacetazine****Pipothiazide****Thioridazine hydrochloride****Group 3: Phenothiazines with a Piperazine Side Chain**

This group is characterized by fewer sedative effects and fewer anti-muscarinic effects than Groups 1 and 2. Extrapyramidal side effects are, however, much more pronounced and frequent.

**Acetophenazine maleate****Butaperazine maleate or phosphate****Carphenazine maleate****Fluphenazine deconatoate, enanthate or hydrochloride****Perphenazine****Pipothiazine palmitate and undecenoate****Prochlorperazine edisylate, maleate and mesylate****Thiethylperazine maleate****Thiopropazate hydrochloride****Thioproperazine mesylate****Trifluoperazine hydrochloride**

The side effects of phenothiazines include sedation, dryness of mouth, potentiation of sedatives and narcotics, hypothermia, postural hypotension, constipation, extra-pyramidal parkinsonian signs, weight increase, skin rashes (including contact dermatitis) and light sensitivity, obstructive jaundice and blood dyscrasias. Continuous use of chlorpromazine over many years has been associated with granular deposits and opacity in the lens and cornea and with skin pigmentation. Chlorpromazine and other phenothiazines alter endocrine function; patients have experienced impotence, amenorrhoea, galactorrhoea, gynaecomastia and weight gain. There have been reports of iatrogenic diabetes mellitus and raised serum cholesterol concentrations. The phenothiazines are epileptogenic and grand mal convulsions are occasionally precipitated.

**II. DRUGS OF OTHER CHEMICAL GROUPS**

These tend to resemble phenothiazines of Group 3 in their actions.

### **1. Butyrophenones and Related Compounds**

**Benperidol**

**Clozapine**

**Droperidol**

**Haloperidol**

**Loxapine**

**Oxypertine**

**Penfluridol**

**Trifluperidol hydrochloride**

The butyrophenones are chemically related to pethidine, and their neuroleptic properties were discovered during a search for analgesic compounds. Haloperidol is the prototype of the series.

Butyrophenones are absorbed promptly and almost completely; peak levels occur in 2–6 hr and excretion is very slow. Cumulation thus occurs readily and this has important consequences on dosage and on interaction with other drugs, especially CNS depressants.

Haloperidol and related compounds produce clinical effects similar to those of the phenothiazines. They have a selective depressant action on the CNS; the actions of dopamine are inhibited and the turnover of dopamine in the brain increased.

Side effects include extrapyramidal symptoms, motor restlessness and dystonic reactions, drowsiness and dizziness. Depression may be worsened. Other side effects are similar to those of the phenothiazines but the butyrophenones are virtually devoid of autonomic side effects.

Penfluridol has a prolonged duration of action; occasional glycosuria has been reported with pimozide and hypersalivation with trifluperidol. Oxypertine releases catecholamines and should therefore not be given concurrently with or within 10–14 days of cessation of treatment with a MAOI drug. Blood counts and liver function tests are desirable for patients on long-term dosage with oxypertine; raised transaminase values have been reported in some patients.

Clozapine has been reported to cause neutropenia, agranulocytosis and pancytopenia, blood counts should be made weekly for the first 18 weeks of treatment and then at least every 2 weeks. Myocarditis has been reported. Circulatory collapse with precipitate hypotension has been reported and for this reason treatment should commence at a low dose (12.5 mg) once or twice per day, then 25–50 mg on the second day, then increasing in steps of 25–50-mg per day over 14–21 days to a 300-mg therapeutic dose in divided doses, 100 mg in the morning 200 mg at bed time. To obtain an optimum effect the dose may have to be increased to a maximum daily dose of 900 mg per day.

Loxapine can cause ocular toxicity, and patients should be regularly observed for pigmentary retinopathy, and lenticular pigmentation (23).

## **2. Thioxanthenes**

**Chlorprothixene**

**Flupenthixol hydrochloride or decanoate**

**Thiothixene hydrochloride**

**Zuclopentixol hydrochloride**

The thioxanthenes (thioxanthines) are a series of compounds structurally similar to the phenothiazines. They retain the sulphur atom but not the nitrogen atom in the middle ring of the phenothiazine nucleus. Thus they provide a parallel series of psychotropic drugs to the phenothiazines.

They have actions and uses as for chlorpromazine but have some antidepressant properties which may lead to insomnia and restlessness. Side effects are similar to those of the phenothiazines.

Some hyperactive patients may be overstimulated by thiothixene; sedation is infrequent and patients may experience insomnia; extrapyramidal symptoms are common with this drug.

## **3. Diphenyl Butylpiperidines**

**Fluspirilene**

**Pimozide**

## **4. Sulpiride and Remoxipride**

Sulpiride and remoxipride are structurally distinct from other antipsychotic drugs. In high doses sulpiride can control the most florid schizophrenic behaviour, but in low doses it has an alerting effect on apathetic withdrawn patients.

Remoxipride is a benzisoxazole derivative and is reported to have a much lesser propensity to cause extrapyramidal side effects than other agents. Its usefulness is curtailed by its propensity to cause blood dyscrasias.

The British National Formulary (4) presents a table of equivalent doses of oral antipsychotic agents but warns that these equivalences are only for guidance.

<b>Antipsychotic</b>	<b>Daily dose</b>
Chlorpromazine	100 mg
Clozapine	50 mg
Haloperidol	2–3 mg
Loxapine	10–20 mg
Pimozide	2 mg
Sulpiride	200 mg
Thioridazine	100 mg
Trifluoperazine	5 mg

## DEPOT INJECTIONS

Depot injections of certain antipsychotic agents have been developed with the objective of ensuring compliance with therapy in schizophrenic patients, and enabling some patients to be released into the community. Depot injections are usually required every 2 or 4 weeks.

Immediately after an injection much higher circulating blood levels of the active agent may occur with an increased incidence of extrapyramidal side effects.

Flupenthixol decanoate	40 mg at 2-week intervals
Fluphenazine decanoate	25 mg at 2-week intervals
Haloperidol decanoate	100 mg at 4-week intervals
Pipothiazide palmitate	50 mg at 4-week intervals
Zuclopentixol decanoate	200 mg at 2-week intervals

There is generally little to choose between these regimes for most patients, but zuclopentixol is said to be more suitable for agitated and aggressive schizophrenics. Flupenthixol can cause increase in agitation and aggressive behaviour in such patients.

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol and other CNS depressant drugs/ antipsychotic agents</b> (6, 8–13, 22, 61)	Alcohol potentiates the effect of the major tranquillisers. Increased CNS-depressant effects may result from combination of drugs sharing pharmacological properties. The effects of narcotic analgesics and the phenothiazines are additive (13).
<b>Antacids/chlorpromazine</b> (1, 2)	Antacids such as aluminium hydroxide decrease the absorption of phenothiazines by forming an absorption complex with them.
<b>Anticoagulant/ phenothiazines</b> (5)	Metabolism of coumarin anticoagulants reduced owing to inhibition of microsomal enzymes by chlorpromazine. Increased laboratory monitoring of prothrombin time needed if this combination is used.
<b>Anticonvulsants/ antipsychotics</b> (74) Phenytoin/ phenothiazines	Antipsychotic agents lower the convulsive threshold  Chlorpromazine and prochlorperazine impair the metabolism of phenytoin and increase the risk of phenytoin intoxication. Other phenothiazine tranquillisers might be expected to interact in the same way.

<i>Combination</i>	<i>Interaction</i>
Carbamazepine/ haloperidol	Carbamazepine accelerates the metabolic breakdown of haloperidol. After stopping carbamazepine it may be necessary to reduce the dose of haloperidol. The dosage of anticonvulsants may need to be increased since haloperidol reduces convulsive threshold.
Phenytoin/clozapine (4)	Phenytoin accelerates the metabolic breakdown of clozapine. Reduced clozapine effect.
Phenytoin/thioridazine (74, 79)	Clinically significant phenytoin intoxication occurred in two cases during concomitant administration of thioridazine. Thioridazine and phenytoin are both metabolized in the liver and each competes with the other for cytochrome P450 hydroxylation; thus the enzyme becomes saturated and phenytoin metabolism is inhibited. Potentiation of effects of phenytoin and increased potential of resulting toxicity have also been reported after the combined use of phenytoin with chlorpromazine or prochlorperazine (74).
	If combined treatment is necessary serum phenytoin concentrations should be monitored and reduction in the phenytoin dosage may be required.
<b>Antidepressants/ antipsychotic agents (8, 54–59)</b>	Increased plasma concentrations of phenothiazines and increased muscarinic effects with tricyclics.
<b>Tricyclics/phenothiazines</b>	Neuroleptic drugs inhibit the metabolism of tricyclic antidepressants in man. Labelled studies with imipramine and nortriptyline showed that excretion of imipramine is diminished while patients were treated concomitantly with perphenazine, haloperidol or chlorpromazine, though not during treatment with flupenthixol. Perphenazine caused decrease of total urinary excretion of nortriptyline, decreased levels of metabolites in plasma and increased plasma levels of unchanged drugs (56).  Combined treatment with neuroleptics and tricyclic antidepressants has been recommended in several clinical reports (57). Tricyclics and phenothiazines are

*Combination**Interaction*

prescribed together in fixed combination, e.g. Motival (nortriptyline plus fluphenazine) and in these doses they do not normally present interaction problems.

Concomitant antipsychotic drugs (16–64 mg perphenazine daily; 6 and 20 mg haloperidol daily, or 12 mg thiothixene daily) given to depressed hospital inpatients receiving desipramine (2.5 mg/kg showed a two- to three-fold increase in plasma mean steady-state desipramine levels when compared with control patients on desipramine alone. Four patients on combined drugs had severe CNS side effects and urinary retention; each had a desipramine plasma concentration in excess of 200 ng/ml (58). Four patients with schizo-affective depression or residual schizophrenia with depression were stabilized on neuroleptic medications of fluphenazine decanoate (12.5 mg/week im) and benztrapine mesylate (2 mg tid), and then given oral imipramine 300 mg daily, following dose titrations over 16 days. In this 6-week clinical trial the combined plasma concentrations of imipramine/desipramine were 189–820 ng/ml (mean 551 ng/ml) on day 21, and 365–2181 ng/ml (mean 850 ng/ml) on day 42. These levels exceeded the therapeutic threshold of 180 ng/ml for combined imipramine/desipramine concentration.

Interaction between neuroleptics and tricyclic antidepressants involves competition for the cytochrome P450 enzyme system which metabolizes both types of compound in the liver. Imipramine has a half-life of 15–20 hr, and an approximate steady state is expected after 5 days' treatment on a standard dose. None of the four patients involved showed a steady state on day 21, in fact two patients showed substantial increases in their imipramine : desipramine ratios between days 21 and 42. This, together with a lower mean combined concentration of the hydroxymetabolites, was suggestive of impaired hepatic metabolism of imipramine, especially since there is no

<i>Combination</i>	<i>Interaction</i>
<b>Antidepressants/ antipsychotic agents <i>cont.</i></b>	documented evidence of competitive enzyme inhibition between benztrapine and tricyclics (59).
MAOI/phenothiazines (70-71)	This combination may lead to hypertension and increased extrapyramidal reactions. The mechanism of this interaction is not known; it is possible that MAOIs inhibit the metabolism of phenothiazines.
MAOI/clozapine (22)	Clozapine enhances the CNS effects of MAOIs
SSRI/haloperidol	Fluoxetine increases plasma concentration of haloperidol and increased incidence of extrapyramidal side effects.
MAOI/oxypterpine (61, 62)	CNS excitation and hypertension caused by this combination.  Some sources have recommended that, since oxypterpine has been observed in animal studies to release small amounts of catecholamines, it should be avoided in patients taking MAOIs.
	This is a theoretical interaction which does not seem to have been reported as being a clinical problem. Although MAOI-adrenaline interaction is likely to be less of a problem than interaction with indirectly acting sympathomimetic agents, there still remains a need for caution when these drugs are used concurrently. It would be wise therefore not to give oxypterpine with MAOIs, or within 3 weeks of the use of MAOIs (62).
<b>Antidiabetic agents/ phenothiazines (6, 11, 22, 63)</b>	Hypoglycaemic effect of sulphonylureas is reduced. Phenothiazines have been reported to cause hyperglycaemia; their mechanism of action in this respect is unknown. No data are available regarding their effects on the control of diabetes, but they should obviously be used with care in the presence of stabilized diabetic treatment. Check frequently for continued diabetic control.

<i>Combination</i>	<i>Interaction</i>
<b>Antihistamines/ antipsychotics (60)</b>	Increased risk of ventricular arrhythmias with astemizole and terfenadine when taken by patients on long-term antipsychotic therapy.
<b>Antihypertensives/ antipsychotic agents</b>	In general, antipsychotic drugs as a group tend to enhance the hypotensive effect of antihypertensive agents. High doses of chlorpromazine antagonize the hypotensive effect of adrenergic neurone blockers.
Methyl dopa/ phenothiazines and haloperidol (10)	Methyl dopa increases the risk of extrapyramidal side effects with phenothiazines and other antipsychotic agents including haloperidol.
<b>Adrenergic neurone- blocking agent/ phenothiazine (6, 8, 10, 11, 64-69)</b>	Reports conflict as to the nature of this interaction. On the one hand, it has been suggested that phenothiazines inhibit the uptake of guanethidine into the adrenergic neurone and thus antagonize its antihypertensive action. This opinion is based upon reports describing several patients on guanethidine who developed exacerbation of their hypertension several days after chlorpromazine was started. Haloperidol and thiothixene also seemed to reverse the effects of guanethidine (64-67). There is a further report of an adrenergic neurone-blocking drug/chlorpromazine interaction in one patient (68). On the other hand, the phenothiazines are reported to potentiate the effects of guanethidine and other hypotensive drugs (69).
<b>Clonidine/phenothiazines pericyazine (11)</b>	The hypotensive effect of clonidine may be neutralized by pericyazine and other drugs in this class.
<b>Corticosteroids/ phenothiazine (1, 2)</b>	Chlorpromazine reduces gut motility and may enhance the absorption of corticosteroids.
<b>Desferrioxamine/ phenothiazines (6, 7, 11)</b>	This combination causes a transient metabolic encephalopathy, characterized by loss of consciousness for 48-72 hr.

<i>Combination</i>	<i>Interaction</i>
<b>Digoxin/phenothiazines</b> (1, 2)	Chlorpromazine reduces gut motility and may enhance the absorption of digoxin.
<b>Disulfiram/ Perphenazine (62)</b>	A psychotic patient was discharged from hospital stabilized on perphenazine (PPZ) (8 mg bid); he was re-admitted 4 weeks later as an emergency after starting treatment with disulfiram. At that time his plasma PPZ concentration was subtherapeutic (1 nmol/l). His dosage of PPZ was doubled without improving his psychotic symptoms but changes in route of dosage to im PPZ enanthate (50 mg/week) resulted in a substantial improvement and an increase in PPZ concentrations to a therapeutic level. It would appear that disulfiram activates the liver enzymes so much that PPZ by mouth is biotransformed into inactive metabolites; parenteral administration of PPZ avoids the 'first pass' effect in the liver.
<b>Food/antipsychotic agents (17–21)</b>	Phenothiazines can be precipitated by many fruit juices, milk, tea and coffee (17). The mixtures are rendered unpalatable and some of the precipitates do not redissolve in hydrochloric acid and so might be expected to be only poorly absorbed <i>in vivo</i> . On this basis it has been variously suggested that tea or coffee might antagonize the efficacy of antipsychotic drug use, especially neuroleptic drugs (18, 19). Support for these views has been given by the results of experiments in rats which suggest that coffee and tea alter the pharmacokinetics of neuroleptic drugs (20). However, in a controlled study in 16 female patients in a psychiatric hospital, the effect of coffee or tea drinking was investigated on steady-state blood levels and clinical efficacy of chlorpromazine, haloperidol, fluphenazine and trifluoperazine (21). Withdrawal of these beverages did not increase the bioavailability of the drugs studied, nor did they affect the individual variation in the plasma levels of these drugs. It was concluded that limitation of coffee or tea intake in medicated psychiatric patients could not be justified (21). It is appreciated, however, that <i>excessive</i> intake of tea

*Combination**Interaction***Levodopa/antipsychotic agents (14, 16)**

or coffee could by their pharmacological effects upset stabilized medication with psychotropic drugs (24).

**Phenothiazines/butyrophenones/thioxanthenes/levodopa**  
Phenothiazines, butyrophenones and thioxanthenes interfere with central amine mechanisms; combinations with levodopa should therefore be avoided where possible. Phenothiazines may reduce the effects of levodopa. *Phenothiazines can cause parkinsonism in their own right.*

It should also be noted that some antihistamines are phenothiazine derivatives (e.g. promethazine, dimethothiazine, methdilazine, trimeprazine) and might therefore be expected to diminish the effects of levodopa if given concomitantly.

**Lithium/antipsychotic agents (3, 25–33)**

Concomitant administration of lithium carbonate and chlorpromazine in normal subjects reduced peak plasma chlorpromazine concentrations to 59.7% of levels with chlorpromazine alone. Area under chlorpromazine concentration-time curve was 26.6% smaller when lithium was taken as well. Since antimanic effects of lithium carbonate may be delayed for 7–10 days after starting treatment, chlorpromazine has been given concurrently for earlier control of manic behaviour. This interaction, however, could explain inadequate responses to therapeutic doses of chlorpromazine. It also explains why there may be sudden onset of chlorpromazine toxicity when lithium is withdrawn. Use such a combination with caution.

Lithium appears to potentiate the neurological complications produced by haloperidol or *vice versa*. The combination has been reported to be complicated by a toxic neurological reaction manifested by rigidity, ataxia and tardive oral dyskinesia (25). Doses of more than 40 mg of haloperidol daily should be avoided when used in combination with lithium.

Existing neuroleptic drug regimens (haloperidol or phenothiazines) in patients with Huntington's chorea

<i>Combination</i>	<i>Interaction</i>
<b>Lithium/antipsychotic agents cont.</b>	<p>seemed to enhance the apparently beneficial response to lithium (26–29). Lithium and phenothiazines are individually liable to induce hyperglycaemia (30–33), although clinical reports have shown a lack of effect of lithium and neuroleptic drug combinations on blood glucose concentrations (33). Lithium has also been reported to be excreted more rapidly during concomitant treatment with chlorpromazine (34).</p> <p>Although it may be necessary to administer haloperidol concurrently with lithium in patients suffering from mania or schizoaffective disorders, this combination should only be used with caution. It is advisable to monitor the clinical state of the patient more frequently when administering mixed doses of haloperidol and lithium (35). Concomitant administration of neuroleptic drugs together with lithium may enhance the beneficial response to lithium in choreiform patients. Lithium–neuroleptic drug combinations do not appear specifically to influence blood sugar levels, although the possibility of an idiosyncratic effect of lithium on blood glucose has been suggested (33).</p>
<b>Lithium/clozapine (22)</b>	Concomitant use of clozapine and lithium increase the risk of development of neuroleptic malignant syndrome which is potentially fatal and presents with hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability.
<b>Metoclopramide/phenothiazines (8)</b>	Concomitant use of phenothiazines and metoclopramide has a greatly increased risk of producing extrapyramidal effects.
<b>Miscellaneous drugs affecting ADH secretion/antipsychotic agents (36)</b>	A drug-induced syndrome of inappropriate secretion of antidiuretic hormone (ADH) has been described secondarily to cyclophosphamide or vincristine therapy. There are other reports on this syndrome

<i>Combination</i>	<i>Interaction</i>
amitriptyline (37) carbamazepine (38) chlorpropamide (39–44) clofibrate (45) cyclophosphamide (46) diuretics (47) fluphenazine (48) haloperidol (49) thioridazine (49) thiothixene (50) vinblastine (51) vincristine (52, 53)	complicating chlorpropamide therapy both in patients with diabetes mellitus (39–41) and in patients with diabetes insipidus (42–44). The syndrome has also been described as occurring with amitriptyline, carbamazepine, clofibrate, diuretics, fluphenazine, haloperidol, thiothixene, thioridazine and vinblastine. Combination of any of these drugs might be expected to increase the likelihood of the syndrome occurring with resulting water retention and natriuresis. Treatment with any combination of these drugs should be used with caution and the syndrome of water intoxication should be borne in mind when any patient presents with symptoms of drowsiness, headache, anorexia, nausea, vomiting, depression and confusion.
<b>Oral contraceptives/ antipsychotic agents (72, 73)</b>	Oestrogen-containing oral contraceptives may potentiate phenothiazine-stimulated prolactin secretion, resulting in mammary hypertrophy and galactorrhoea.
<b>Skeletal Muscle Relaxants/antipsychotic agents (76–78)</b>	There is some evidence that the phenothiazines lower serum and erythrocyte cholinesterase levels. Methotriimeprazine has been reported to prolong tubocurarine-induced muscle relaxation, and the possibility of interaction with suxamethonium has been suggested. Promazine has been shown to give rise to prolonged apnoea when administered during surgery to a patient who had received suxamethonium.
	Phenothiazines should be administered with caution to patients who have received suxamethonium.
<b>Plastic intravenous delivery systems/ phenothiazines (75)</b>	The loss of 45 drugs (including chlorpromazine hydrochloride, promazine hydrochloride, thioridazine hydrochloride and trifluoperazine dihydrochloride) during simulated infusions through plastic infusion sets has been attributed to sorption processes.

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## **4.2 INTERACTIONS WITH DRUGS USED IN THE TREATMENT OF DEPRESSIVE ILLNESS**

Drugs used in the treatment of depressive illness can be classified into three main groupings (1) monoamine oxidase inhibitors (MAOIs), (2) tricyclic antidepressants and related compounds; and (3) selective serotonin reuptake inhibitors (SSRIs). Finally, there is a small group of active substances that are used in the treatment of depressive illness that can be placed together as (4) miscellaneous.

### **1. MAOI ANTIDEPRESSANTS**

*INN name:*

**Iproniazid phosphate**

**Isocarboxazid**

**Mebanazine**

**Moclobemide**

**Nialamide**

**Phenelzine sulphate**

**Tranylcypromine sulphate**

**Pargyline**

#### **Uses**

Monoamine oxidase inhibitors (MAOIs) by inhibiting monoamine oxidase cause an accumulation of amine neurotransmitters. The metabolism of some amine drugs, such as indirect acting sympathomimetic amines, is also inhibited and their pressor effect may be potentiated. The pressor effect of tyramine in cheese, yeast extracts, fermented soya bean products, beers, Chianti and other red and white wines, and pickled herrings is dangerously potentiated.

Monamine oxidase inhibitors are now used much less frequently than tricyclic antidepressants and SSRIs because of the dangers of dietary and other drug interactions.

Phobic patients, depressed patients with atypical, hypochondriacal or hysterical features are said to respond best to MAOIs.

Most MAOIs bind irreversibly to monoamine oxidase sub-types A and B so that the enzyme is inactivated, reversal of the MAOI effect only occurs when new enzymes are synthesized. *Moclobemide* is claimed to bind reversibly to monoamine oxidase sub-type A and also to cause less potentiation of the pressor effects of

tyramine, but patients should nevertheless be advised to avoid tyramine-containing foods.

### Recorded Interactions

<i>Combination</i>	<i>Interaction</i>
<b>MAOI antidepressant/alcohol (1)</b>	Hypertensive reactions may occur due to the tyramine (or other pressor amine) content of some alcoholic drinks, notably beers including alcohol-free and low-alcohol beers (2, 3) and wines. The belief that the interaction with wine only occurred with rough red wines of the Chianti type has been shown to be wrong. Interactions may occur with both red and white wines (2).  Advise avoidance of all alcoholic beverages since it is unlikely that the patient will be able to determine the tyramine content of the drink.
<b>MAOI antidepressant/anaesthetic (4)</b>	Anaesthesia may be potentiated. Vasopressor drugs in local anaesthetic preparations (adrenaline, noradrenaline) will interact to give hypertensive crisis. Normally this does not present an anaesthetic problem; however, phentolamine may have to be given.
<b>MAOI antidepressant/anticoagulant (5, 6)</b>	MAOIs potentiate the anticoagulant action of coumarins and may cause severe haemorrhage. This interaction is due to inhibition of coumarin metabolism.  Avoid this combination. If interaction occurs with haemorrhage treat with vitamin K.
<b>MAOI antidepressant/antihypertensive agent guanethidine, methyldopa (7–9)</b>	MAOIs may antagonize the hypotensive effects of guanethidine and diminish those of methyldopa. The use of these antihypertensive agents like that of MAOI is declining, but the interaction is of clinical significance.
<b>MAOI antidepressant/appetite suppressant (9–13) amphetamine sulphate</b>	Phenylpropanolamine-containing appetite suppressants have been available in the USA, UK and Australia and are available as nasal decongestants. All these appetite suppressants have an indirect sympathomimetic activity; concomitant administration

<i>Combination</i>	<i>Interaction</i>
benzphetamine hydrochloride	may cause severe hypertensive episodes with cerebrovascular accidents leading to hemiplegia, coma and even death.
chlorphentermine hydrochloride	Hyperpyrexia may also be a complication of the interaction. Severe hyperpyrexia has been reported (18) within hours after the ingestion of tranylcypromine 10 mg plus a capsule containing dextro-amphetamine and amobarbital; fever 43°C (109°F) was accompanied by agitation, hyperkinesis, coma, opisthotonus and convulsions. The patient responded to supportive measures and was discharged without significant residua 20 days later. Cardiac arrhythmias have also been reported from this type of interaction. A considerable number of adverse reactions, mainly hypertensive episodes, have been reported in association with phenylpropanolamine-containing appetite suppressants from Australia.
dexamphetamine sulphate	Appetite suppressants containing sympathomimetic amines, particularly those containing phenylpropanolamine, should not be given to a patient being treated with a MAOI drug or within 2 weeks of stopping such treatment. These agents would best be regarded as obsolete.
diethylpropion hydrochloride	<i>Note: In the event of hypertensive crisis use phentolamine do not use any other antihypertensive agent.</i>
fenfluramine hydrochloride	
methylamphetamine hydrochloride	
phendimetrazine tartrate	
phenmetrazine hydrochloride	
phenmetrazine theoclinate	
phentermine	
<b>MAOI antidepressant/mazindol (15)</b>	Mazindol, an anti-obesity agent, does not inhibit monoamine oxidase but potentiates the pressor action of catecholamines. It can therefore be anticipated that it will interact with MAOIs. MAOI should not be given concomitantly with mazindol. A month at least should be allowed between stopping either of the agents and starting the other.
<b>MAOI antidepressant/ barbiturate hypnotic (16)</b>	Potentiation of barbiturates can be expected.
<b>MAOI antidepressant/caffeine or other xanthine (17)</b>	Patients on MAOI antidepressants may exhibit hyperexcitability reactions including insomnia after consuming caffeine- (or other xanthine-) containing

<i>Combination</i>	<i>Interaction</i>
<b>MAOI</b> <b>antidepressant/caffeine or other xanthine</b> <i>cont.</i>	medicines or beverages. Caffeine is a common constituent of many proprietary analgesic preparations.
<b>MAOI</b> <b>antidepressant/insulin and antidiabetic agents</b> (18–24)	MAOIs enhance or prolong the hypoglycaemic responses to both insulin and the sulphonylureas. It is not known whether the biguanides and glynmidine are similarly affected, although this is a possibility since it has been postulated that MAOIs interfere with the compensatory adrenergic response to hypoglycaemia (20).
<b>MAOI antidepressant/anti-parkinsonian drugs</b> (10,21) benzhexol hydrochloride (trihexyphenidyl hydrochloride USP) benztropine mesylate biperiden hydrochloride or lactate caramiphen hydrochloride chlorphenoxamine hydrochloride dicyclomine hydrochloride ethopropazine hydrochloride hyoscyamine sulphate methixene hydrochloride orphenadrine hydrochloride or citrate procyclidine hydrochloride	MAOIs non-specifically inhibit liver microsomal enzymes. This potentiates the action of co-administered anticholinergic agents, especially those used in the treatment of parkinsonism. MAOIs should be given with caution to patients receiving anticholinergic drugs; the dosage of the latter may have to be reduced. Dry mouth, blurred vision, urinary hesitancy or retention and constipation would be evidence of this interaction.
<b>MAOI</b> <b>antidepressant/levodopa</b> (22, 23)	Severe headache, flushing of the face, hypertension or hypertensive crisis may follow from the use of this combination. It is likely that these adverse cardiovascular effects are due to increased storage and release of either, or both, dopamine and nor-

<i>Combination</i>	<i>Interaction</i>
<b>MAOI antidepressant/muscle relaxant</b> <b>Phenelzine/</b> <b>suxamethonium (25)</b>	<p>adrenaline. In contrast, reports suggest that tricyclic antidepressants, notably amitriptyline and imipramine, are safe for patients on levodopa treatment for parkinsonism (23, 24).</p> <p>Phenelzine sulphate has been reported to cause a reduction in the level of plasma pseudocholinesterase. Prolonged apnoea in a patient on phenelzine has been reported after suxamethonium administration. There is no evidence at present that other MAOIs affect pseudocholinesterases.</p>
<b>MAOI antidepressant/sympathomimetic amines</b> (10, 11, 14, 26–35) bronchodilators adrenaline ephedrine isoetharine isoprenaline methoxyphenamine methylephedrine orciprenaline phenylephrine phenylpropanolamine pseudoephedrine rimiterol salbutamol terbutaline e.g. nasal decongestants ephedrine hydroxyamphetamine methoxamine naphazoline oxymetazoline phenylephrine phenylpropanolamine pseudoephedrine tetrahydrozoline tuaminoheptane xylometazoline	<p>Adrenergic effects are potentiated, resulting in severe headache, hypertension or hypertensive crisis.</p> <p>Cardiac arrhythmias and circulatory insufficiency may result from this interaction with central excitation if compounds pass the blood–brain barrier. Hyperpyrexia may also occur, especially with tranylcypromine and amphetamine-like compounds. This hyperpyrexia may be accompanied by convulsions and coma. Deaths have been reported from this type of interaction.</p> <p>Indirectly acting sympathomimetic amines are absolutely contraindicated in patients being treated with a MAOI antidepressant or within 2 weeks of stopping such treatment. It would be wise to avoid all sympathomimetic amines in combination with MAOIs. A patient being treated with phenelzine (15 mg tid.) experienced a severe throbbing frontal headache 15 min after taking 32 mg of phenylpropanolamine (component of Mucron) to alleviate ‘head cold’ symptoms. Blood pressure rose to 210/100 mmHg and the patient was admitted to hospital with a suspected subarachnoid haemorrhage (34).</p> <p>In a further case of sudden severe headache, confirmed as subarachnoid haemorrhage with the possibility of a left posterior angiotensin communicating aneurysm, phenelzine–phenylpropanolamine interaction was implicated (35). Two other cases have been reported (29) in which MAOI antidepressants and phenylpropanolamine (slow-release dosage forms) interacted to evoke severe headache or status</p>

<i>Combination</i>	<i>Interaction</i>
<i>NB: some of the above listed agents are in non-prescription 'cold remedies'</i>	epilepticus, but with only slight elevation of blood pressure. A marked rise in blood pressure has been shown experimentally using phenylpropanolamine (free-form) in subjects taking MAOIs (33).
e.g. hypertensive agents mephentermine metaraminol methoxamine noradrenaline oxedrine	<i>Treatment of interaction:</i> (i) $\alpha$ -adrenergic blocking drugs (e.g. phentolamine for the hypertensive crisis). Only in severe cases should (ii) $\beta$ -adrenergic blocking drugs (e.g. propranolol be used for tachycardia and cardiac arrhythmias; or (iii) chlorpromazine for CNS effects be considered since both these agents themselves interact with MAOIs.
<b>MAOI</b> <b>antidepressant/SSRI</b> <b>antidepressant</b> (36–40)	Fluoxetine has a half-life of 1–3 days and its active metabolite norfluoxetine has a mean half life of 9.3 days. At least 14 days should elapse between discontinuation of a MAOI and initiation of treatment with fluoxetine. At least 5 weeks should elapse if fluoxetine has been prescribed chronically or at high dose between discontinuation and initiation of MAOI treatment. Serious and fatal reactions including hyperthermia, rigidity, myoclonus autonomic instability, delirium and coma have been reported with concomitant use of SSRI and MAOI, or when an inadequate interval has been allowed between stopping one treatment and starting the other. Similar advice is given for fluvoxamine, paroxetine and sertraline.
<b>MAOI</b> <b>antidepressant/tricyclic</b> <b>antidepressant</b> (41–51) e.g. amitriptyline butriptyline clomipramine desipramine dibenzepin dothiepin doxepin imipramine iprindole	Although reports of interactions between all MAOIs with all the individual tricyclic antidepressants have not been made, there is adequate evidence to consider that this is a generally undesirable and hazardous combination. Flushing, sweating, excitability, muscle twitching, tremor, rigidity and opisthotonus, clonic and tonic convulsions, hyperpyrexia, loss of consciousness, coma and ultimately death appear to be the general course in the worst cases. The mechanism involved in this interaction is thought to be a MAOI-induced block of enzymes normally metabolizing the tricyclic compounds.

<i>Combination</i>	<i>Interaction</i>
maprotiline nortriptyline opipramol protriptyline tofenacin trimipramine viloxazine	Normally absolute contraindication: severe reactions may result from the concomitant administration of these antidepressants and from commencement of tricyclic antidepressant therapy within 2 weeks of stopping MAOI drugs. However, some psychiatrists have maintained that combined MAOI-tricyclic treatment is often effective when either group alone has failed, and that with care in regulating dosage, severe reactions can be avoided (52-54).
<b>Phenelzine/imipramine (60)</b>	An 18-year-old in-patient treated for anorexia nervosa with phenelzine (30 mg bid) and trimipramine (150 mg at night) experienced an adverse reaction featuring hypothermia when imipramine 150 mg was substituted for trimipramine. She developed nausea, loss of reality, was mentally impaired, disorientated, restless, with an axillary temperature of 37.8°C, while her skin was pale, cold and cyanosed. Her pupils were dilated; she was hypertonic and displayed extensor plantar reflexes. She improved and recovery was uneventful. This combination is contraindicated.
<b>MAOI antidepressant/tryptophan (56, 57)</b>	There have been several case reports of reactions similar to the serotonin syndrome in patients receiving MAOIs together with tryptophan, i.e. a reaction characterized by drowsiness, unsteadiness, hyperreflexia and ataxia. The patient appearing to be inebriated. If tryptophan is added to a patient on a MAOI it is advisable to commence dosage at 0.5 g/day and gradually increase the dose over several weeks to the routine dose of 6.0 g/day. Such treatment should be initiated in hospital (58). Controlled trials of tryptophan with tricyclic antidepressants have produced equivocal results (59).
<b>MAOI antidepressant/tyramine- (or other pressor amine-) containing foodstuffs</b>	Tyramine acts as an indirectly acting sympathomimetic amine. Hypertensive episodes may occur (see previous entry in this section on interactions with sympathomimetic amines). Fatalities have been

<i>Combination</i>	<i>Interaction</i>
(12, 26, 46, 60–77)	reported with some of these drug–food interactions
e.g. tyramine-containing	(notably with cheese).
avocado pears (74)	Patients on MAOI antidepressants must be advised on
broad-bean pods	diet and warned to avoid consuming foods known to
beers, including	be rich in tyramine (or other pressor amine) content.
alcohol free or	<i>Note: the α-blocking drug phentolamine is of value in</i>
low-alcohol beers	<i>the treatment of hypertensive episodes.</i>
(2, 3)	
Bovril	
canned figs	
caviar (75)	
unprocessed cheese	
(especially	
Cheddar	
and Gruyère)	
Chianti, red and	
white wines and	
sherry	
game	
New Zealand prickly	
spinach	
( <i>Tetragonia</i>	
<i>tetragonoides</i> ) (76)	
pickled herring	
yeast products	
(including	
Marmite)	
e.g. serotonin-	
containing	
bananas (17)	

## 2. TRICYCLIC, POLYCYCLIC AND OTHER ANTIDEPRESSANTS

*INN Name:*

**Amitriptyline hydrochloride**

**Amoxapine**

**Butriptyline hydrochloride**

**Citalopram hydrobromide**

**Clomipramine hydrochloride**

**Desipramine hydrochloride**

**Dibenzepin hydrochloride**

**Dothiepin hydrochloride**

**Doxepin hydrochloride**  
**Imipramine hydrochloride**  
**Iprindole hydrochloride**  
**Lofepramine hydrochloride**  
**Maprotiline hydrochloride**  
**Mianserin hydrochloride**  
**Nomifensine maleate**  
**Nortriptyline hydrochloride**  
**Opipramol hydrochloride**  
**Protriptyline hydrochloride**  
**Tofenacin hydrochloride**  
**Trazodone hydrochloride**  
**Trimipramine maleate**  
**Viloxazine hydrochloride**

The early compounds in this class all had a three-ring structure, however the title is now a misnomer as there are now 1-, 2-, 3- and 4-ring structures with broadly similar properties. These drugs are most effective for treating moderate to severe endogenous depression.

Agitated and anxious patients tend to respond best to the sedative compounds, whereas those that are withdrawn and apathetic to the less sedating compounds. Tricyclic antidepressants with sedative properties include amitriptyline, mianserin, trazodone and trimipramine. Less sedative agents include amoxapine, desipramine, imipramine, iprindole, lofepramine, nortriptyline, and viloxazine. Protriptyline has a stimulant action.

Tricyclic antidepressants are also effective in the management of panic disorders. Oral and facial pain may respond to tricyclic antidepressants.

Tricyclic antidepressants may also be used in the treatment of nocturnal enuresis in children and have a role in the treatment of anorexia nervosa.

The mechanism of action of the polycyclics and the related compounds is complex and multidirectional and by no means fully established. Current theories of antidepressant action circulate around: (i) amine re-uptake; (ii) monoamine oxidase inhibition; (iii) central histamine receptor blockage; and (iv) altered post-synaptic receptor sensitivity. The second of these theories is particularly interesting and it has been advanced as a possibility since tricyclics such as amitriptyline and imipramine do inhibit MAO activity *in vitro*. It may be possible that this is another aspect of the mechanism underlying re-uptake inhibition since MAO is tightly bound to mitochondrial membrane. These theories are discussed fully in the excellent review by King on developments in antidepressant medication (78).

CNS depressant drugs are related in chemical structure and are mainly dibenzazepine or dibenzo-cycloheptane derivatives; because of their structure they are commonly known as *tricyclic* (polycyclic would be a better term), although they

might be more accurately classified according to their effect on biogenic amine re-uptake, e.g.

<i>Selective noradrenaline re-uptake inhibitors</i>	<i>Selective 5HT re-uptake inhibitors</i>	<i>Noradrenaline and dopamine re-uptake inhibitor</i>	<i>Weak or non-re-uptake inhibitors</i>
Maprotiline <sup>+</sup>	Clomipramine <sup>+</sup>	No example	Doxepin <sup>+</sup>
Desipramine <sup>+</sup>	Trazodone*	since removal of Nomifensine	Iprindole <sup>+</sup>
Viloxazine	Citalopram		Mianserin*
Nizoxetine**			

<sup>+</sup>Also anticholinergic; \*5HT receptor antagonist; \*\*Not in UK. Classification based on King (79).

Iprindole (pramidole), tofenacin, trazodone and viloxazine have slightly different chemical structures from typical tricyclic compounds, zimelidine was a bicyclic compound (a pyridylallylamine derivative), but was removed from the UK market in 1983 and maprotiline and mianserin have a tetracyclic structure. Nomifensine had an unusual tetrahydroisoquinoline structure but like the tricyclics it blocked noradrenaline uptake and dopamine re-uptake; this latter unique property had led to trials in parkinsonism but without success. It was removed from the UK market in 1986. All these compounds, however, have similar uses to those of the classic tricyclic antidepressants and it is convenient, if not strictly accurate, to continue to classify them under this general heading.

### Side Effects

*Arrhythmias* and heart block may follow the use of tricyclic antidepressants, particularly amitriptyline, and may be a factor in the sudden death that may occur with these compounds

*Blood dyscrasias*: these agents have been reported to cause blood dyscrasias, particularly mianserin. In the case of mianserin a full blood count is recommended every 4 weeks during the first three months of treatment.

*Convulsions*: maprotiline has been associated with convulsions. Overdosage with amoxapine has been associated with seizures.

*Tardive dyskinesia*: amoxapine has been reported to cause tardive dyskinesia.

*Malignant neuroleptic hyperpyrexia*: amoxapine has been reported to be associated with this potentially fatal syndrome which is characterized by hyperpyrexia, muscle rigidity.

*Endocrine changes:* amoxapine has been reported to cause increased prolactin secretion, breast enlargement and galactorrhoea in women.

*Epilepsy:* tricyclic and related antidepressants lower the convulsive threshold and should be prescribed with extreme caution in epileptics.

*Glaucoma, urinary retention, ileus:* the tricyclic compounds possess cholinergic blocking activity as well as  $\alpha$ -adrenergic blocking activity; they therefore produce enhanced effects in patients receiving atropine-like anticholinergics, antihistamines, phenothiazines (tranquillizers and antihistamines) and anti-parkinsonian drugs. The mechanism involves additive effects at receptor sites, and the consequences of this type of interaction are significant in the geriatric patient who is prone to glaucoma, urinary retention and adynamic ileus.

*Hepatic damage:* mianserin has been reported to cause liver damage and jaundice.

*Priapism:* trazodone has been associated with priapism.

## Drug Interactions

<i>Combination</i>	<i>Interaction</i>
<b>Tricyclic antidepressant/adrenaline and noradrenaline (50, 80–85)</b>	<p>An enhanced cardiovascular effect may occur due to the tricyclic drug inhibiting the uptake of noradrenaline into sympathetic neurones. Hazardous cardiovascular effects in the form of arrhythmias and dysrhythmias may occur in patients receiving adrenaline or noradrenaline in local anaesthetic formulations used in dentistry (86).</p> <p>Treatment with tricyclic antidepressant drugs is a contraindication to the use of adrenaline, noradrenaline or other sympathomimetic amine (87). This includes adrenaline or noradrenaline in local anaesthetic formulations which should not be given within 10 days of stopping tricyclic antidepressants.</p>
<b>Tricyclic antidepressant/ alcohol (88–90)</b>	<p>Enhanced sedation, inhibition of intestinal movement and fatty changes in the liver are consequences of this interaction. Ability to drive or operate machinery may be grossly impaired. Patients being treated with tricyclic antidepressants who take alcohol may show both unusual and unexpected behavioural disorders. These are usually most noticeable during the first few days of tricyclic therapy (91).</p> <p>Amitriptyline and alcohol are contraindicated in</p>

<i>Combination</i>	<i>Interaction</i>
<b>Tricyclic antidepressant/ alcohol cont.</b>	patients who might perform hazardous tasks such as driving or operating factory machinery (92).
<b>Tricyclic antidepressant/ anticholinergic drugs (93)</b> e.g. anti-emetic agents (including proprietary motion sickness remedies) antihistamines atropine-like drugs anti-parkinsonian drugs orphenadrine (mephenamine) (94-97)	This combination results in additive anticholinergic effects at the receptor site. Adverse effects are usually minor (dry mouth, constipation, blurred vision, etc.) however, in geriatric patients there is the danger of precipitating urinary retention, acute glaucoma or adynamic ileus. The possibility of this interaction should be anticipated especially in elderly patients. The danger of self-medication with non-prescription motion sickness remedies should be stressed. <i>Note: Promethazine, methdilazine, and trimeprazine are phenothiazine derivatives and anticholinergic effects may be more pronounced with combinations involving these drugs.</i>
<b>Tricyclic antidepressant/MAOI antidepressant (41-51)</b>	Although reports of interactions between all tricyclics with individual MAOI antidepressants have not been made, there is adequate evidence to consider that this is a generally undesirable and hazardous combination. Flushing, sweating, excitability, muscle twitching, tremor, rigidity and opisthotonus, clonic and tonic convulsions, hyperpyrexia, loss of consciousness, coma and ultimately death appear to be the general course in worst cases. The mechanism involved in this interaction is thought to be a MAOI-induced block of enzymes normally metabolizing the tricyclic compounds. Avoid using tricyclics for at least 2 weeks after stopping MAOI.
<b>Tricyclic antidepressant/SSRI antidepressant (38, 97)</b>	Fluoxetine increases the plasma levels of tricyclic antidepressants due to inhibition of hepatic cytochrome P450 11DS. Theoretically, this may lead to enhanced tricyclic toxicity.
<b>Tricyclic antidepressant/ antihistamine (102)</b>	Antihistamines will augment the anticholinergic effects of tricyclic antidepressants. The mechanism involves additive effects at receptor sites. Adverse effects are usually minor (dry mouth, constipation, blurred vision,

*Combination**Interaction*

etc.); however, in geriatric patients there is the danger of precipitating urinary retention, acute glaucoma or adynamic ileus. N.B. promethazine, methdilazine and trimeprazine are phenothiazine derivatives and anticholinergic effects may be more pronounced with combinations involving these.

With the newer non-sedating antihistamines there is an increased risk of ventricular arrhythmias with astemizole and terfenidine (13)

**Tricyclic antidepressant/antihypertensive agent**  
(50, 103–113)

Bethanidine, debrisoquine and guanethidine are concentrated in adrenergic neurones by an active uptake mechanism, and owe their hypotensive action to this selective concentration. This uptake mechanism is inhibited by tricyclic antidepressants.

Introduction of desipramine to clonidine treatment in a controlled study led to loss of blood pressure control in four out of five hypertensive patients (112)

**Tricyclic antidepressant/baclofen**  
(Lioresal) (117)

Nortriptyline and imipramine, separately, apparently potentiated the antispastic effect of the skeletal muscle relaxant, baclofen, in one patient. Prior treatment for 18 months with baclofen produced good relief of spasticity and left the patient with sufficient muscle tone to stand. However, 50 mg nortriptyline daily at bed time after 6 days caused increasing weakness of the legs and he was unable to stand. Muscle tone returned after withdrawal of nortriptyline. Two weeks later imipramine 75 mg daily caused the same loss of muscle tone.

**Tricyclic antidepressant/barbiturate hypnotic**  
(118)

Barbiturates stimulate the metabolism of tricyclic antidepressant drugs and thereby reduce their efficacy. The tricyclic antidepressants may be ineffective in the presence of barbiturates. If the barbiturates are withdrawn the patient may become overdosed. Management is to stop barbiturates and reduce tricyclic dosage.

<i>Combination</i>	<i>Interaction</i>
<b>Tricyclic antidepressant/calcium, channel blockers</b> e.g. amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, verapamil	Diltiazem and verapamil increase plasma concentrations of imipramine and possibly other tricyclics (114).
<b>Tricyclic antidepressant/antiepileptic agents</b> (98–101)	Tricyclic antidepressants lower the convulsive threshold and should be prescribed with extreme caution to epileptics.
<b>Tricyclic antidepressant/ H<sub>2</sub>-receptor-antagonists cimetidine</b>	Cimetidine is a known inhibitor of hepatic metabolism of drugs, and symptoms of tricyclic toxicity have been reported in patients receiving cimetidine concurrently with either desipramine or imipramine (119). Elevated tricyclic concentrations during combined therapy or reductions in tricyclic concentrations after withdrawal of cimetidine have been reported for imipramine (120) and nortriptyline (121). Studies in healthy subjects have also indicated increased bioavailability and/or impaired hepatic metabolism of doxepin (122, 123) and imipramine (124) during cimetidine therapy. Adjustment of tricyclic dosage may be required if cimetidine therapy is initiated or discontinued. Ranitidine or a proton pump inhibitor, e.g. omeprazole, may be preferred since neither alter the pharmacokinetics of doxepin or imipramine (124).
<b>Tricyclic antidepressant/levodopa</b>	Although tricyclic antidepressants have been used safely with levodopa (23), hypertensive crises have occurred in patients receiving amitriptyline or imipramine with the peripheral dopa decarboxylase inhibitor carbidopa (125, 126). Imipramine has also been reported to impair the rate of levodopa absorption, presumably due to its muscarinic properties (127).
<b>Tricyclic antidepressant/antimalarial</b> (115)	There is an increased risk of ventricular arrhythmia with halofantrine.

<i>Combination</i>	<i>Interaction</i>
<b>Tricyclic antidepressant/ antipsychotic drug (116)</b> e.g. perphenazine, haloperidol, thiothixene	Interaction between neuroleptics and tricyclic antidepressants involves competition for the cytochrome P450 enzyme system, which metabolizes both types of compounds in the liver. Severe CNS side effects and urinary retention may be precipitated.
<b>Tricyclic antidepressant/ orphenadrine (mephenamine) (94–96)</b> orphenadrine citrate orphenadrine hydrochloride	The anticholinergic effects of tricyclic antidepressants and orphenadrine summate. Enhanced side effects (dry mouth, constipation, blurred vision) may be expected. The danger of precipitating urinary retention, acute glaucoma or adynamic ileus in elderly patients should not be overlooked.
<b>Tricyclic antidepressant/ sympathomimetic amines (32, 85)</b>	The pressor responses to sympathomimetic amines is increased in patients receiving antidepressants. Even the levels of noradrenaline in local anaesthetics have produced fatal hypertensive crises. Imipramine potentiates the action of isoprenaline. The administration of imipramine (25 mg tid) to 10 chronic asthmatic patients using isoprenaline aerosols gave subjective improvement and increased peak expiratory flow. Cardiovascular responses to isoprenaline were also potentiated.

### 3. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

*INN name:*

**Fluvoxamine maleate**  
**Fluoxetine**  
**Paroxetine**  
**Sertraline**

Selective serotonin reuptake inhibitors are indicated for the treatment of depressive illness. Fluoxetine is also used in the treatment of bulimia nervosa, where the recommended dosage is 60 as opposed to 20 mg/day initially for the treatment of depressive illness.

#### **Side Effects**

Asthenia, fever, nausea, diarrhoea, dry mouth, appetite loss, dyspepsia, vomiting.

Headache, nervousness, insomnia, tremor, dizziness, decreased libido with delayed or inhibited orgasm (128, 129).

Hypomania or mania.

Dyskinesia with buccal-lingual-masticatory syndrome; movement disorders; worsening of pre-existing movement disorders including those associated with neuroleptic drug; seizures.

Blood dyscrasias have been reported but causality has not been established.

Rashes, allergic reactions, angioneurotic oedema, urticaria.

SSRIs impair the ability to drive and operate machinery.

SSRIs have also been demonstrated in milk and should not be administered to nursing mothers.

Withdrawal symptoms have been reported with paroxetine; it should not be discontinued abruptly (130).

The overall safety of SSRIs has been reviewed in depth by Mitchell (131).

#### **Extent of Clinical Use**

Fluvoxamine, fluoxetine, paroxetine and sertraline accounted for 0.09, 1.03, 0.77 and 0.48% of the cost of all NHS prescriptions written on FP10 or GP10 in the United Kingdom in 1994 or 2.37% (£93 million) of the total FHSA medicines bill.

#### **General Information**

Fluvoxamine can prolong the elimination of drugs metabolized by oxidation in the liver and interactions with warfarin phenytoin and theophylline can be clinically significant. Paroxetine interacts with phenytoin to reduce plasma concentrations of paroxetine. It may also interact with warfarin to produce increased bleeding in the presence of unaltered prothrombin times. Sertraline is highly bound to plasma proteins and may interact with other highly protein-bound drugs, such as digoxin, phenytoin and warfarin (38).

#### **Reported Drug Interactions (40, 132–134)**

	<i>Combination</i>	<i>Interaction</i>
<b>SSRI/Anticonvulsants</b>		The convulsive threshold is lowered by fluoxetine and other SSRIs and epileptic fits have been precipitated in patients whose epilepsy has previously been well controlled. However, the plasma concentration of carbamazepine and phenytoin are raised by concomitant administration of fluoxetine and

<i>Combination</i>	<i>Interaction</i>
<b>SSRI/Antidepressants monoamine oxidase inhibitors (36–40, 131)</b>	fluvoxamine. Phenytoin lowers the plasma concentration of paroxetine.
	Fluoxetine has a half life of 1–3 days and its active metabolite norfluoxetine has a mean half-life of 9.3 days. At least 14 days should elapse between discontinuation of monoamine oxidase inhibitor (MAOI) and initiation of treatment with fluoxetine. At least 5 weeks should elapse if fluoxetine has been prescribed chronically or at high dose between discontinuation and initiation of MAOI treatment. Serious and fatal reactions including hyperthermia, rigidity, myoclonus autonomic instability, delirium and coma have been reported with concomitant use of SSRI and MAOI, or when inadequate interval has been allowed between stopping one treatment and starting the other. Similar advice is given for paroxetine and sertraline (135).
<b>SSRI/Antidepressants tricyclics (38, 97, 136, 137)</b>	Fluoxetine increases the plasma concentrations of tricyclic antidepressants due to inhibition of hepatic cytochrome P450 IIIDS. Theoretically this may lead to increased tricyclic toxicity.
<b>SSRI/antiarrhythmic agents (40)</b>	Plasma concentrations of flecainide and encainide are increased by fluoxetine and fluvoxamine (40).
<b>SSRI/carbamazepine (138)</b>	The addition of fluvoxamine to a constant dose of carbamazepine may lead to increased plasma levels and carbamazepine intoxication (138).
<b>SSRI/cyclosporin (162)</b>	A 59-year-old patient underwent cardiac transplant for end-stage heart failure. Cyclosporin was given as an immunosuppressant, and he was maintained on 225 mg twice daily, with a stable trough whole blood concentration of 300 mg/l. Seventeen days post-operatively the patient developed acute depression and was given the SSRI fluoxetine 20 mg once daily. After 10 days trough cyclosporin concentration had risen to 588 mg/l and the dose of cyclosporin was reduced to 75 mg twice daily. He did not respond to the SSRI which was discontinued and trough cyclosporin level

<i>Combination</i>	<i>Interaction</i>
<b>SSRI/cyclosporin</b> <i>cont.</i>	fell to 95 mg/l after 7 days, necessitating an increase in cyclosporin dosage to 200 mg twice daily which once again gave trough levels of 300 mg/l.
<b>SSRI/dopaminergic drugs</b> (140, 141)	Hypertension and CNS excitation has been seen when fluoxetine and other SSRIs have been given in conjunction with selegiline, an irreversible type B selective MAOI, used in the treatment of parkinsonism (140, 141).
<b>SSRI/lithium</b> (37, 142–145)	Cases of lithium neurotoxicity with marked somnolence and absence of seizures have been reported to be induced by fluoxetine and fluvoxamine given concomitantly with lithium salts (142–145). A syndrome of convulsions and hyperpyrexia has also been reported when SSRIs have been co-administered with lithium salts (37). Frequent monitoring of lithium plasma levels may be necessary.
<b>SSRIs/phenytoin</b> (146)	Fluoxetine inhibits the hepatic metabolism of phenytoin and has been reported to raise plasma phenytoin levels leading to neurotoxicity (146).
<b>SSRI/propranolol</b> (147)	Fluvoxamine interaction studies in man have shown that co-administration with propranolol increases propranolol blood levels. A complete heart block occurred in a patient on propranolol and fluoxetine (147).
<b>SSRI/sumatriptan</b> (148)	Concurrent administration of SSRI with the selective antimigraine serotonin agent, sumatriptan, causes increased risk of CNS toxicity (148). The combination should be avoided.
<b>SSRI/theophylline</b> (150, 161)	Plasma concentrations of theophylline are increased by fluvoxamine. The pharmacokinetic interaction between fluvoxamine and theophylline is due to potent inhibition of CYP1A2 by fluvoxamine. The result is potential theophylline toxicity (161). A toxic interaction has been reported in a child (150).

<i>Combination</i>	<i>Interaction</i>
<b>SSRI/tryptophan (151)</b>	SSRIs in animal studies have been shown to induce "serotonin syndrome" comprising restlessness, agitation, severe gastrointestinal symptoms including diarrhoea (151). Fluoxetine if given with tryptophan in the treatment of depression causes agitation and severe nausea (40).
<b>SSRI/vinblastine (160)</b>	Impaired metabolism of vinblastine and increased toxicity (160).
<b>SSRI/warfarin (152, 153)</b>	Fluoxetine and sertraline bind to plasma proteins; fluoxetine has been reported to increase plasma warfarin concentrations leading to excessive anticoagulation (152, 153). Fluoxetine has been demonstrated to increase bleeding in warfarin treated patients in the presence of an unaltered prothrombin times (134).

#### 4. OTHER AGENTS

*INN name:*

**Flupenthixol**

**Tryptophan**

Flupenthixol is a neuroleptic of the thioxanthene series. It has antidepressant properties and, at the lowdoses of 1–3 mg/day used for this purpose, side effects are less than with tricyclic antidepressants.

Tryptophan appears to benefit some patients with resistant depression. Tryptophan products were withdrawn from the European, USA and Japanese markets in late 1989 following association with the eosinophilia-myalgia syndrome (154). They have recently been reintroduced into the UK under carefully monitored conditions.

#### Recorded Interactions

<i>Combination</i>	<i>Interaction</i>
<b>Flupenthixol/antidepressants</b>	Interactions at the low doses used in the treatment of depression are not a clinical problem.
<b>Flupenthixol/antiparkinson agents</b>	However, the anticholinergic effects of tricyclic antidepressants and antiparkinsonian drugs may be increased and tardive dyskinesia be precipitated (155).

<i>Combination</i>	<i>Interaction</i>
<b>Flupenthixol/ antihypertensives</b>	Flupenthixol antagonizes the blood pressure lowering effects of adrenergic blocking agents such as guanethidine, possibly also clonidine (155).
<b>Flupenthixol/tea or coffee</b>	Support for a suggested interaction was given by studies in rats which suggested that tea and coffee altered the pharmacokinetics of neuroleptic drugs (156). Additional support was given by <i>in vitro</i> studies showing precipitation of the neuroleptic and the strong complex formed with tannins (157); however, a controlled trial in psychiatric patients failed to show any effect of tea or coffee drinking on steady-state blood levels and clinical efficacy of a number of neuroleptics (158). However the psychotropic effects of caffeinated drinks cannot be neglected (159).
<b>Tryptophan/ antidepressants</b>	CNS excitation and confusion with MAOIs. Agitation and nausea with the SSRIs fluoxetine, fluvoxamine, paroxetine and sertraline (40). Danger of a 'serotonin syndrome' (151).

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## **4.3 DRUG INTERACTIONS WITH LITHIUM SALTS**

Lithium salts are used in the prophylaxis and treatment of mania, and in the prophylaxis of manic depressive illness (bipolar illness or bipolar depression) and in the treatment of recurrent depression (unipolar illness or unipolar depression).

Lithium treatment is unsuitable for children. Lithium therapy should *never* be instituted where there are no facilities for *regular* monitoring of plasma lithium levels which should not be allowed to exceed  $1.3 \text{ mmol Li}^+/\text{l}$ ; and the normal therapeutic range is between  $0.4$  and  $1.0 \text{ mmol Li}^+/\text{l}$ .

Side effects of lithium treatment are related to dosage and to the degree of accumulation in intracellular and extracellular body fluids; they are more common during the first weeks of treatment and usually disappear when the dose is reduced and include transient nausea, fine tremor and weakness. Polydipsia and polyuria may occur and are thought to be due to interference by lithium of the activation of cyclic  $3', 5'$ -AMP by the antidiuretic hormone (1-3). Lithium-induced diabetes insipidus is a recognized complication and, under these circumstances, thiazide diuretics can exert an antidiuretic effect and elevate plasma lithium levels and produce intoxication. More serious effects are likely if the plasma lithium level reaches  $1.5 \text{ mmol Li}^+/\text{l}$  in which case treatment should be stopped immediately. Symptoms and signs of lithium toxicity include ataxia, coarse tremor, confusion, vomiting, diarrhoea, thirst and dryness of mouth, drowsiness and slurred speech. Non-toxic goitre and impairment of thyroid function detectable by biochemical tests but without clinical manifestations have been reported (4-7), as has also severe hypothyroidism of rapid onset during a short course of lithium treatment (8); the plasma-bound iodine level returned to normal after lithium was stopped.

Plasma concentrations in excess of  $2.0 \text{ mmol Li}^+/\text{l}$  require emergency treatment with forced diuresis or dialysis if severe lithium toxicity is to be avoided or minimized. Severe lithium intoxication results in coma with hyper-reflexia, muscle tremors, attacks of hyperextension of the limbs and occasionally epileptic seizures; deaths have been reported.

The drug is contraindicated in heart failure, impaired renal function, Addison's disease and in conditions of disturbed sodium balance. It is suggested that it should not be given during pregnancy; elderly patients may not tolerate lithium well and adverse effects suggestive of neurotoxicity are currently causing much concern (9, 10). Over-reliance on frequent serum lithium determinations should be avoided (10); the best way to avoid serious sequelae from neurotoxicity in the elderly patient treated with lithium is to monitor the patient carefully and frequently for the signs and symptoms of those disorders (10).

*Different formulations of lithium vary widely in bioavailability, a change in formulation requires the same precautions as initiation of treatment. Patients stabilized on a particular formulation and dosage should not have their formulation altered. This is one circumstance where patients should be made aware of the differences between brand names and the importance of adhering to one formulation, and doctors should prescribe by brand name.*

## LITHIUM CARBONATE

The usual lithium salt given is lithium carbonate. The following formulations are available on the UK market:

<b>Camcolit</b>	250 mg (6.8 mmol) and 400 mg (10.8 mmol)
<b>Liskonium</b>	450 mg (12.2 mmol)
<b>Phasal</b>	300 mg (8.1 mmol)
<b>Priadel</b>	200 mg (5.4 mmol) and 400 mg (10.8 mmol)

## LITHIUM CITRATE

<b>Li-liquid</b>	509 mg/5 ml (5.4 mmol/5 ml)
<b>Litarex</b>	564 mg (6 mmol)
<b>Priadel liquid</b>	520 mg/15 ml (5.4 mmol/5 ml)

In France lithium preparations, such as lithium gluconate are additionally available, and in Germany lithium salts may be presented additionally as gluconate, orotate, and acetate salts.

<i>Combination</i>	<i>Interaction</i>
<b>Aminophylline theophylline/lithium (11–12)</b>	Lithium excretion is increased and lithium serum levels are reduced resulting in decreased efficacy of treatment.
<b>Antacids/lithium (13–15)</b>	Sodium bicarbonate increases the excretion of lithium leading to lowering of plasma lithium levels and reduced therapeutic efficiency (13). Antacids containing combinations of aluminium and magnesium hydroxides and dimethicone were without effect on the <i>in vitro</i> dissolution (14) and the <i>in vivo</i> bioavailability of lithium carbonate (15).
<b>Antibacterials/lithium metronidazole (16)</b>	Two women experienced toxic reactions to long-term lithium treatment following the brief use (1 week) of metronidazole to treat vaginitis (16). In the first patient, lithium blood levels and serum creatinine

<i>Combination</i>	<i>Interaction</i>
	<p>levels were elevated and the patient complained of polyuria and nocturia with a 24-hr urine volume of 6.8 l. Creatinine levels remained elevated (180 mmol/l) for 5 months after metronidazole was stopped. In the second case, serum sodium levels rose and the patient became confused and needed assistance when walking. Diagnosis of nephrogenic diabetes insipidus was made. Lithium was stopped but hypernatraemia (up to 180 mmol/l) and abnormally dilute urine (averaging 300 mOsm/l) continued for the next 6 months.</p>
<b>Spectinomycin (17, 18)</b>	Lithium toxicity has been reported on isolated occasions in patients receiving spectinomycin (17) and tetracycline (18).
<b>Tetracycline (18–20)</b>	<p>Two days after starting a course of long acting capsules of tetracycline (250 mg tid (Terabid), a 30-year-old woman, maintained on lithium carbonate sustained-release tablets (800 mg bid) and having a serum lithium concentration of 0.5–0.84 mmol/l, experienced a sharp rise in serum lithium to 1.7 mmol/l. Two days later it rose to 2.74 mmol/l and the patient was drowsy, with slurred speech and a fine tremor of the hands. She was very thirsty. Her serum lithium fell slowly over the next few days after the two drugs were withdrawn. Interaction was attributed to the nephrotoxic effect of tetracycline (18). In contrast, lithium and tetracycline have been used concomitantly in many patients without serious problems and, additionally, tetracycline has been used to treat the acneform skin eruptions induced by lithium (19). Lithium blood concentrations were decreased rather than increased in healthy subjects following addition of tetracycline (20). Caution should be exercised whenever lithium is combined with any drug that may affect renal function. Frequent monitoring of lithium, creatine and electrolyte levels and urine osmality may also aid the rapid recognition of patients developing renal complications.</p>

<i>Combination</i>	<i>Interaction</i>
<b>Antidepressants/lithium MAOIs (21, 22)</b>	The Committee on Safety of Medicine (CSM) has warned that enhanced serotonergic effects may result when lithium is combined with monoamine oxidase inhibitors and other antidepressants (see entries below in this section). Fatal adverse effects have been reported in a patient receiving fluoxetine, tranylcypromine and tryptophan along with other multiple drug therapies (21). At least 14 days should elapse between discontinuation of a MAOI and the introduction of fluoxetine. Because of the long half-lives of fluoxetine and its metabolite norfluoxetine, it is also advised that at least 5 weeks should elapse between discontinuation of fluoxetine and introduction of a MAOI antidepressant (22).
<b>SSRIs</b>	The CSM has warned that enhanced serotonergic effects may result from combination therapy of highly selective serotonin re-uptake inhibitors such as fluoxetine and fluvoxamine, with lithium and other antidepressants (monoamine oxidase inhibitors, tryptophan). Although such enhancement may be beneficial in some instances, it can produce a life-threatening serotonin syndrome comprising hyperthermia, tremor and convulsions. The CSM has received 19 reports of adverse reactions where patients were concomitantly treated with fluvoxamine and lithium; five of these reports concerned convulsions and one report was associated with hyperpyrexia (23). Such combination therapy should be used with extreme caution.
<b>Tricyclics (3, 4, 24)</b>	Eight patients suffering from a major unipolar depression and having failed to respond to treatment for 3 weeks or more with tricyclic antidepressants were given lithium. All eight patients experienced a remarkable relief of their depression within 48 hr (3, 4). This rapid antidepressant effect of lithium in 'treatment-resistant' patients might be due to the enhancement of the central serotonergic system unveiling the tricyclic antidepressant-induced sensitization of the serotonergic postsynaptic receptors. Serious neurotoxic effects are a risk and

<i>Combination</i>	<i>Interaction</i>
	the combination should be used with extreme care. For example, epileptic seizures have been reported in one patient receiving amitriptyline when lithium was added (24).
<b>Tryptophan (23, 25)</b>	The CSM has warned that enhanced serotonergic effects may result when lithium is combined with tryptophan and other antidepressants (see earlier entries in this section) (23). It should be recalled that L-tryptophan has been implicated in an acute eosinophilia-myalgia syndrome which resulted in its withdrawal from the US and UK markets in 1989. It has since been re-introduced in the UK under carefully monitored conditions for use in the treatment of depressed patients unresponsive to other therapy (see review (25)).
<b>Antiepileptic agents/lithium carbamazepine (26–30)</b>	Lithium is known to have an epileptogenic effect even when used in normal therapeutic doses (26, 27). It is not surprising therefore that neurotoxicity may occur with carbamazepine without increased plasma lithium concentrations. Patients experienced ataxia, dizziness, blackout, agitation and restlessness, confusion and feelings of unreality when carbamazepine was introduced into an established lithium regimen. Symptoms disappeared when carbamazepine was withdrawn (28, 29). For example, a 22-year-old woman with bipolar affective disorder developed severe neurotoxic symptoms when treated with a combined regimen of lithium carbonate and carbamazepine in therapeutic doses. An open trial of the two medications separately and concurrently implicated a synergistic interaction between the two (30).
<b>Phenobarbitone phenytoin (31, 32)</b>	Severe CNS toxicity despite ‘normal’ serum lithium concentrations has been described in two patients taking phenytoin alone or together with phenobarbitone (31, 32).
<b>Antihypertensives/lithium ACE inhibitor (33, 34)</b>	Lithium toxicity has been described in two patients after therapy with enalapril. In the first case it was

<i>Combination</i>	<i>Interaction</i>
<b>Antihypertensives/lithium ACE inhibitor cont.</b>	thought that lithium retention was due to the increase in sodium excretion induced by enalapril. The second case was thought to be due to dehydration and volume deficit, caused by a gastrointestinal upset, being aggravated by enalapril on the renin-angiotensin-aldosterone axis in which the homeostatic response to extracellular volume loss had become impaired (33, 34).
<b>Ca<sup>2+</sup> channel blockers (35–38)</b>	Neurotoxicity has been reported in one patient receiving lithium following the addition of verapamil (35). Serum lithium concentrations were inside the accepted therapeutic range and it was thought that the similar actions of lithium and verapamil on neurosecretory processes were responsible for the interaction. Verapamil has also been reported to decrease serum lithium concentrations (36). Neurotoxicity has also been reported in a patient receiving lithium and diltiazem as well as other drugs (37), but the evidence was weak and other explanations could account for the interaction (38).
<b>Methyldopa (19, 39, 41)</b>	Lithium toxicity induced by concurrent administration of methyldopa has been described on a number of occasions.
<b>Antineoplastic agents (cisplatin)/lithium (42, 43)</b>	Cisplatin has been reported to alter the proximal tubular reabsorption of calcium and magnesium. Lithium, being also reabsorbed in the proximal tubules is a likely candidate for drug interaction. The hypothesis was tested in a 36-year-old woman who was maintained on lithium carbonate (300 mg qid) and required cisplatin (100 mg/m <sup>2</sup> , followed by i.v. mannitol and fluids) for cancer of the tongue. The lithium dose was kept constant. Her serum lithium fell from 1.0 to 0.3 mEq/l during the first course and from 0.8 to 0.5 mEq/l during the second. These decreases were transient being reversed in 2 days. The relative contribution of the cisplatin and the forced diuresis to the presumed increase in lithium clearance is unknown (42).

<i>Combination</i>	<i>Interaction</i>
	<p>There are theoretical reasons and some clinical data to indicate that serum lithium levels fall when cisplatin is given. This effect appears to be rapidly reversed but it may be important when high-dose cisplatin is repeated frequently. Lithium levels should be carefully monitored under such circumstances (43).</p>
<b>Antipsychotic agents/lithium chlorpromazine (44–46)</b>	<p>Since the antimanic effect of lithium carbonate may be delayed for 7–10 days after starting treatment, chlorpromazine has been given concurrently for earlier control of manic behaviour. Lithium has been reported to be excreted more rapidly during concomitant treatment with chlorpromazine (44). Concomitant administration of lithium carbonate and chlorpromazine in normal subjects reduced peak plasma chlorpromazine concentrations to 59.7% of levels with chlorpromazine alone. Area under the chlorpromazine concentration-time curve was 2.6% smaller when lithium was taken as well (45). This interaction may explain inadequate responses to therapeutic doses of chlorpromazine. It may also explain why there may be a sudden onset of chlorpromazine toxicity when lithium is withdrawn (46). Use this combination with caution.</p>
<b>Haloperidol and other phenothiazines (47–64)</b>	<p>There have been isolated reports of neurotoxicity of brain damage (delerium, seizures, encephalopathy, increased incidence of extrapyramidal symptoms) in patients receiving lithium concomitantly with flupenthixol (47), fluphenazine (48), high doses of haloperidol (49–51) or thioridazine (52, 53). However, retrospective studies have failed to detect such adverse interactions in patients receiving lithium and neuroleptics concomitantly (54, 55). It has been suggested (56) that neurotoxicity induced by lithium and neuroleptics is a rare entity, about 40 cases being reported in the literature. There is controversy whether the combination produces any greater risk than either agent alone and there is controversy over whether the neurotoxicity is a distinct diagnostic entity</p>

<i>Combination</i>	<i>Interaction</i>
<b>Haloperidol and other phenothiazines cont.</b>	or simply represents atypical cases of either lithium toxicity or the neuroleptic malignant syndrome.
	Existing neuroleptic drug regimens, usually haloperidol or phenothiazines, were continued in patients with Huntington's chorea started on lithium therapy. These drugs seemed to enhance the apparently beneficial response to lithium (57–60). Lithium and phenothiazines are individually liable to induce hyperglycaemia (61–64), although clinical reports have shown a lack of effect of lithium and neuroleptic drug concentrations on blood glucose levels (64).
<b>Cholinergic agent/lithium (65)</b>	Lithium antagonizes the effect of neostigmine and pyridostigmine. Lithium therapy has also been reported to unmask previously undiagnosed myasthenia gravis.
<b>Diuretics/lithium carbonic anhydrase inhibitor (11, 66)</b>	Acetazolamide impairs the proximal tubular reabsorption of lithium ions and increases their renal excretion. This increased lithium excretion could impair the antipsychotic effect (11), although the diuretic action of acetazolamide is short-lived and the interaction may therefore be transient (66).
<b>Loop diuretics (66–67)</b>	Frusemide, bumetanide and ethacrynic acid seem less likely to cause lithium retention than the thiazides, although caution is warranted especially with patients on restricted dietary sodium (66, 67). Amiloride and possibly other potassium-sparing diuretics have no effect on lithium excretion.
<b>Thiazides (66–67)</b>	Thiazide diuretics produce sodium depletion by inhibiting distal tubular sodium reabsorption. The consequent increase in proximal tubular reabsorption frequently results in an increase in plasma lithium concentrations (66). Patients who are stabilized on lithium therapy and begin taking thiazide diuretics are at significant risk of developing lithium toxicity. The development of toxicity depends upon pre-diuretic lithium

<i>Combination</i>	<i>Interaction</i>
<b>General advice on use of diuretics in patients on lithium (66–69)</b>	concentrations, diuretic dose, and the degree of dietary sodium restriction (67).
<b>Ispaghula husk/lithium (70)</b>	If diuretic therapy is necessary in patients stabilized on lithium, the lithium dose should be reduced by 25–50% (66–68) and lithium concentrations should be measured twice weekly until re-stabilization occurs. Loop diuretics may be preferable. Lithium–diuretic interactions and the precautions required have been reviewed (69).
<b>NSAIDs/lithium (72–83)</b>	There has been one report of a possible interaction between lithium and ispaghula husk (a bulk-forming laxative). Ispaghula might have inhibited the intestinal absorption of lithium resulting in low serum concentrations. Other bulk-forming laxatives may also inhibit the intestinal absorption of lithium (70).
<b>Skeletal muscle relaxants/lithium</b>	<p>Decreased clearance and increased serum concentrations of lithium resulting in toxicity on some occasions have been reported after concomitant prescription of lithium with diclofenac (71), ibuprofen (72, 73), indomethacin (74, 75), naproxen (76), piroxicam (77, 78) and these should be avoided in patients taking lithium. Secondary sources have also implicated ketoprofen and phenylbutazone (79). However, serum lithium concentration is not increased by sulindac (76, 80, 81). Serum lithium concentrations were increased in one patient receiving aspirin (82) but this has not been confirmed by others and an interaction is considered unlikely (75, 83).</p> <p>Paracetamol is the preferred agent for mild occasional aches, pains and fever in patients receiving lithium, although occasional doses of aspirin are acceptable. Sulindac appears to be the safest NSAID for long-term use. If it is necessary to use any of the other NSAIDs then the maintenance dose of lithium should be reduced (84).</p>
	Prolonged neuromuscular blockade has been reported following the use of <i>d</i> -tubocurarine (65), pancuronium

<i>Combination</i>	<i>Interaction</i>
<b>Skeletal muscle relaxants/lithium cont.</b>	bromide (85), and succinylcholine (86) in patients receiving lithium.
<b>Weight reducing regimens/lithium</b>	Some patients have taken a lithium diet to avoid weight gain, but this can lead to lithium toxicity. This has been reported to be enhanced by the use of mazindol, a centrally acting anorectic agent (87).

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## **4.4 DRUG INTERACTIONS WITH AGENTS USED IN THE TREATMENT OF EPILEPSY**

The choice of anti-epileptic agent to use is largely dictated by the nature of the seizures and the age of the patient. The following recommendations reflect current consensus.

**Tonic clonic seizures** (Grand mal epilepsy): the drugs of choice are carbamazepine, phenytoin and sodium valproate. Phenobarbitone and primidone are also effective but sedating.

**Absence seizures** (petit mal): the drugs of choice are ethosuximide or sodium valproate.

**Myoclonic seizures**: sodium valproate is the drug of choice, clonazepam and ethosuximide or other antiepileptic agents may be tried.

**Absence seizures, atonic and tonic seizures**: epilepsy of this type is usually a problem of childhood, and may be seen in isolation as specific epileptic syndromes or as part of a more generalized problem of cerebral damage and mental retardation.

Phenytoin, sodium valproate, clonazepam, ethosuximide or any other of the antiepileptic agents specified below may be tried.

Acetazolamide or corticosteroids may be useful adjuncts.

*As a general principle single therapy treatment should always be tried first, in all patients with epilepsy, the use of therapeutic cocktails are a secondary step after attempts to control the condition with single agents has not given adequate effect.*

**Epilepsy in children**: Appleton writing in *The Prescribers' Journal* (1995) states "Broadly speaking, sodium valproate is currently the first choice for generalized seizures and epilepsy syndromes, and carbamazepine for partial seizures and syndromes. Phenobarbitone and phenytoin should never be the drugs of first choice in view of their adverse cognitive and cosmetic effects". These views are in accord with those of Verity *et al.* (1).

**Use of anti-epileptic agents in old age**: the incidence and prevalence of epilepsy increase with old age. Stolarek *et al.* (2) reported a survey of 411 consultant geriatricians which represented 53% of those contacted to complete a questionnaire exploring current British approach to treating epilepsy in old age. Only 58% of those responding said they would initiate anti-epileptic treatment themselves, only 16% would initiate treatment after the first seizure, 59% after the second and 5%

after the third. Phenytoin was the first choice for generalized tonic-clonic seizures with carbamazepine the second. If good control was not obtained 67% would substitute with another first line anticonvulsant, while 27% would add a second drug. Less than 3% would use the newer anticonvulsants lamotrigine or vigabatrin.

## **1. HYDANTOINS**

**Ethotoin**

**Methoin**

**Phenytoin sodium**

## **2. OXAZOLIDINES**

**Paramethadione**

**Troxidone**

## **3. SUCCINIMIDES**

**Ethosuximide**

**Methsuximide**

**Phensuximide**

## **4. PHENACETYLUREA DERIVATIVES**

**Phenacetamide**

**Pheneturide**

## **5. LONG-ACTING BARBITURATES AND RELATED COMPOUNDS**

**Methylphenobarbitone**

**Phenobarbitone**

**Primidone**

## **6. BENZODIAZEPINES**

**Clonazepam**

**Diazepam**

**Lorazepam**

**Nitrazepam**

## **7. OTHER ESTABLISHED AGENTS**

**Beclamide**

**Carbamazepine**

**Chlormethiazole**

**Sodium valproate**  
**Sulthiamé**

## 8. NEWER AGENTS

**Lamotrigine**

Lamotrigine was developed as a folate antagonist following suggestions that folate antagonism, a property of phenytoin and other hydantoins, might be the mode of their anticonvulsant action. This hypothesis has been discredited and lamotrigine has turned out to be a useful anti-epileptic agent, not by folate antagonism but by acting on fast sodium channels in the presynaptic nerve terminals, resulting in inhibition of the release of glutamate, the major excitatory transmitter. Lamotrigine has a broad spectrum of anti-epileptic effect. Its use is as an adjunctive treatment of partial seizures and secondary generalized tonic clonic seizures not adequately controlled with other anti-epileptics.

Lamotrigine is conjugated to a glucuronide in the liver, it has a 24-hr elimination half-life in healthy volunteers. Lamotrigine is about 50% bound to plasma proteins.

Allergic skin reactions occur in a small percentage of patients. Rare instances of Stevens-Johnson syndrome have been reported.

**Vigabatrin**

Vigabatrin was designed as an inhibitor of the enzyme GABA-transaminase; this action causes an increase in the concentration of the inhibitory transmitter GABA. It is indicated for the use as an add-on treatment for epilepsy not satisfactorily controlled by other anti-epileptic agents, particularly in the therapy of partial and secondary generalized tonic-clonic seizures. It can worsen myoclonic and absence seizures.

Vigabatrin was originally called gamma-vinyl GABA and had a delayed development due to the observation that it produced vacuolation in the brains of animals in the toxicological evaluation studies. This has now been demonstrated to be intramyelinic oedema and is not thought to be relevant for man.

Vigabatrin is not metabolized and has an elimination half-life of 7–8 hr. It is not protein bound and does not induce hepatic cytochrome P450 or other drug-metabolizing enzymes. Interactions with other drugs are therefore unlikely. In clinical studies a gradual reduction of about 20% in plasma phenytoin concentration has been observed. The mechanism is unknown, but is not thought to be of clinical significance.

**Gabapentin**

Gabapentin is a structural analogue of GABA and was developed as a GABA antagonist. Gabapentin is not a GABA antagonist but is an effective antiepileptic agent by a mechanism as yet not fully elucidated. It binds firmly to a peptide binding

site in the brain. Its use is as an adjunct to the treatment of partial seizures with or without secondary generalization, not satisfactorily controlled with other epileptics.

Gabapentin is excreted unchanged in the urine. It has an elimination half-life of 5–7 hr.

Plasma protein binding is negligible.

*It is important to note that none of these three newer antiepileptic agents are as yet currently recommended for single therapy treatment.*

Single therapy studies on all three of these agents are underway. Vigabatrin has been shown to be particularly effective in infantile spasms, particularly those associated with tuberous sclerosis where it may become accepted as the drug of choice.

### **Tiagabine**

Tiagabine has a novel mechanism of action: inhibition of GABA re-uptake. In placebo-controlled trials tiagabine was associated with a 50% or greater reduction in seizure rate in 24% of patients with complex partial seizures, in 32% of patients with simple partial seizures and in 45% of patients with secondary generalization. Tiagabine has been filed for marketing approval in USA and Denmark.

### **Felbamate**

Felbamate (2 phenyl-1–3 propanediol dicarbamate) is a unique antiepileptic agent.

## **MAJOR SOURCES OF INTERACTIONS AMONGST ANTI-EPILEPTIC AGENTS**

### **Phenytoin and Phenobarbitone**

The vast majority of drug interactions with anticonvulsant drugs occur with phenytoin and with phenobarbitone. Phenytoin is metabolized by hepatic microsomal enzymes to an inactive parahydroxylated derivative which is excreted in the bile and urine as the glucuronide. This metabolic route accounts for 60–70% of the administered dose; 5% is excreted unchanged in the urine and approximately 30% is excreted as other metabolites. The metabolites of phenytoin excreted in the bile are resorbed from the intestine and elimination of the drug is delayed.

The enzymes which metabolize phenytoin can be saturated, and many of the drugs interacting with phenytoin do so by saturating this mechanism, therefore these reactions are most critical in patients who require high doses of phenytoin to control their epilepsy. The effects of phenytoin are enhanced by those drugs which diminish its metabolism in the liver or impair liver function; the effects are diminished by drugs which induce enzymic activity in the liver.

Phenytoin sodium diffuses across the placenta and caution should be exercised in its use during pregnancy; it is found in the milk of nursing mothers. Phenytoin

should be administered with caution to patients receiving thyroid replacement therapy, since phenytoin is known to displace thyroxine from plasma protein binding, thus elevating the free thyroxine level. Some patients taking phenytoin have demonstrated a megaloblastic anaemia associated with a low serum folate level; phenytoin has been shown in both *in vitro* and *in vivo* studies to inhibit the intestinal conjugase necessary for the conversion of dietary folic polyglutamates into readily absorbable free folic acid.

Toxic effects of treatment with phenytoin sodium are of fairly frequent occurrence and are occasionally severe. The milder effects can usually be overcome by reduction of dosage for a few days and then gradual restoration up to the original dosage; these effects include dizziness, nausea and skin rashes. Tenderness and hyperplasia of the gums are frequent occurrences, especially in younger patients. Hirsutism is a less frequent effect, but is most noticeable in young females. Other adverse reactions include tremors, fever, vomiting, blurring of vision, ataxia, mental confusion and hallucinations. Leucopenia, pancytopenia, exfoliative dermatitis and purpura: these effects are always severe and may necessitate immediate withdrawal of the drug. Lupus erythematosus and widespread lymphadenopathy accompanied by fever, hepatomegaly and splenomegaly have been very occasionally reported.

Phenytoin sodium is strongly alkaline (pH about 11–12) in solution and may cause gastric irritation; this can be prevented to some extent by taking the dose with at least half a glassful of water after meals. However, the therapeutic effect is greatest if dosage is taken before meals.

Phenobarbitone is mainly excreted unchanged in the urine; it is only about 40% bound to plasma proteins and about 10% of a dose is metabolized to an inactive hydroxyl derivative and excreted in the urine with the unchanged drug. It is a weak acid and thus is excreted more rapidly at high urinary pH and more slowly at low pH. It has two main roles in drug interactions; first, it induces liver microsomal enzymes and thus will reduce the activity of a range of other drugs including phenytoin by enhancing their metabolism. The concomitant administration of phenytoin with phenobarbitone in epilepsy reduces the level of phenytoin in the plasma to below that attained when phenytoin is given alone. Fortunately this alteration in phenytoin metabolism does not seem to be a problem in the management of the epileptic patient since phenobarbitone also possesses anticonvulsant activity. Its second role in drug interactions is that its CNS-depressant action augments the effect of any other CNS-depressant drug.

Other anticonvulsant drugs do not figure in reported cases of drug interaction to any significant extent; carbamazepine has close structural similarity to the tricyclic antidepressants, and it has been suggested that it may therefore be dangerous in patients receiving MAOI antidepressants although no clinical reports of such interaction have appeared. Sulthiame appears to inhibit the metabolism of diphenylhydantoin by the liver, which prolongs its half-life and increases its plasma level. This interaction has been demonstrated in the clinic and could be of importance if the drugs are used in combination in epilepsy. The benzodiazepines would appear to have little effect on liver microsomal enzymes and do not enter into those

interactions common to drugs with enzyme-inducing properties. Biological studies of sodium valproate indicate that it produces an increase in the level of aminobutyric acid (GABA) in the brain by inhibiting GABA transaminase, the enzyme responsible for the breakdown of GABA. However, there is no simple correlation between convulsive activity and GABA levels, although evidence linking them is growing. Sodium valproate may enhance the sedative effects of other drugs and potentiate MAOIs and thymoleptics. False positives may occur in urine testing for diabetics. The compound has been shown to be teratogenic in animals and should be avoided in women of child-bearing age unless possible benefits outweigh this hazard.

## I. DRUG INTERACTIONS WITH PHENYTOIN

### 1. Drugs which Enhance the Effects of Phenytoin

These drugs set out on the table below have been reported, sometimes in single or isolated cases (\*), to potentiate the effects of phenytoin and so increase the risks of intoxication. They interact with phenytoin by a number of mechanisms including liver enzyme inhibition and displacement from plasma-protein binding. Details of some of the interactions in this category are given below. See also review articles on drug interactions with phenytoin (50, 51).

<b>Aspirin</b> (3, 4)	<b>*Methylphenidate</b> (36)
<b>Azaptopazone</b> (5, 6)	<b>*Oestrogens</b> (13)
<b>Chloramphenicol</b> (7, 10)	<b>Oral contraceptives</b> (37)
<b>Chlordiazepoxide</b> (11)	<b>Pheneturide</b> (11)
<b>*Chlorpheniramine</b> (12)	<b>Phenylbutazone</b> (38, 39)
<b>Cimetidine</b> (14–16)	<b>Phenyramidol</b> (40, 41)
<b>Co-trimoxazole</b> (17)	<b>*Prochlorperazine</b> (13)
<b>Dexamethasone</b> (20, 21)	<b>*Propranolol</b> (29)
<b>*Dextropropoxyphene</b> (propoxyphene) (22, 23)	<b>Sulphadiazine</b> (17)
<b>Diazepam</b> (11)	<b>Sulphamethizole</b> (17)
<b>Dicoumarol</b> (24)	<b>Sulphaphenazole</b> (17)
<b>Disulfiram</b> (25–28)	<b>Sulthiame</b> (42–44)
<b>*Fruusemide (furosemide)</b> (29)	<b>*Thioridazine</b> (45)
<b>*Halothane</b> (30)	<b>Thyroid hormones</b> (46)
<b>Isoniazid (in slow inactivators)</b> (31–34)	<b>Tolbutamide</b> (47)
<b>Lithium</b> (35)	<b>Viloxazine</b> (48)
	<b>*Warfarin</b> (48)

<i>Combination</i>	<i>Interaction</i>
<b>Aspirin/phenytoin</b> (4)	Aspirin, in healthy subjects, caused 27% increase in free phenytoin fraction in plasma at 4 hr and reduced

<i>Combination</i>	<i>Interaction</i>
	48-hr area under curve (AUC) for total phenytoin by 19%: free phenytoin AUC values were unchanged. More rapid clearance of total phenytoin probably compensated for salicylate displacement of phenytoin from plasma binding.
	Total phenytoin concentrations for therapeutic monitoring must be interpreted cautiously when patients also receive salicylates. Interaction does not necessitate modification of phenytoin dosage (4).
<b>Azapropazone/phenytoin (5, 6)</b>	<p>A change from fenclofenac to azapropazone (600 mg bid) to control a flare-up of arthritis evoked neurological toxicity and hospitalization in an epileptic patient stabilized on phenytoin and primidone (5). Competition by the two drugs for hepatic hydroxylation systems is the likely mechanism of this interaction.</p> <p>A grand mal epileptic, who had received maintenance treatment with phenytoin 300 mg tid for 3 years, developed increasing confusion, nausea, diplopia, nystagmus and vertigo 2 weeks after starting azapropazone 600 mg twice daily. His condition returned to normal when both drugs were stopped, and later phenytoin was restarted without recurrence of toxicity (6). A follow-up study in five normal subjects showed that azapropazone (600 mg bid) caused plasma phenytoin concentrations to double and two subjects showed severe drowsiness (6).</p>
<b>Antibiotics and Antibacterials/phenytoin</b>	
<b>Chloramphenicol/ phenytoin (7-10)</b>	<p>Nine out of 20 patients receiving chloramphenicol and phenytoin simultaneously experienced CNS toxicity of phenytoin; tetracyclines plus phenytoin in 19 patients gave no toxic symptoms.</p> <p>Chloramphenicol is known to block metabolism of phenytoin by liver enzymes (9). Chloramphenicol given to a patient stabilized on phenytoin and phenobarbitone caused the serum concentration of phenytoin to increase from 10.8 to 30.5 µg/ml. Dosage</p>

<i>Combination</i>	<i>Interaction</i>
<b>Chloramphenicol/ phenytoin cont.</b>	of the two anticonvulsants had to be reduced by 25% to reduce adverse effects (10).
<b>Erythromycin/phenytoin (52)</b>	There is limited evidence of an interaction with erythromycin (52), but this was subject to considerable interindividual variation and is of unknown clinical significance.
<b>Isoniazid/phenytoin (53–55)</b>	The interaction with isoniazid is well documented and potentially significant in slow acetylators of isoniazid. Some 10–20% of subjects receiving this combination may develop raised phenytoin concentrations and signs of toxicity (53, 54). At least one case was fatal (55). The effect is due to inhibition of hepatic microsomal enzymes by isoniazid; poor metabolizers of isoniazid may develop sufficient blood isoniazid concentrations for this inhibition to become marked.
<b>Metronidazole/phenytoin (56–59)</b>	Conflicting results have been reported with metronidazole (56, 57), while a fall in serum phenytoin concentrations and a loss of seizure control has been reported in a patient in whom nitrofurantoin was added to therapy (58). A combination of impaired absorption and impaired metabolism of phenytoin was suggested as the cause of this interaction. A similar mechanism has been proposed for an interaction between oxacillin and phenytoin which resulted in one patient developing status epilepticus (59).
<b>Rifampicin/phenytoin (60–62)</b>	Rifampicin can reduce plasma phenytoin concentrations and markedly increase its clearance (60, 61). When given together with isoniazid and phenytoin it will override the effect of isoniazid on phenytoin even in slow acetylators (61). Various sulphonamides are reported to interact with phenytoin reducing its clearance and prolonging its half-life (62).
<b>Cimetidine/phenytoin (14–16, 100)</b>	In four studies cimetidine (900–1000 mg daily) produced a 13, 28, 60 or 100% increase in serum phenytoin concentrations in epileptic patients. Four of 14 patients exhibited rash or CNS signs of phenytoin

<i>Combination</i>	<i>Interaction</i>
	intoxication. Cimetidine inhibited the hepatic hydroxylation of phenytoin.
<b>Dexamethasone/phenytoin (20–21)</b>	Although it is established that dexamethasone blood concentrations are decreased by concomitantly administered phenytoin (20), it is not well known that this steroid can evoke an increase in phenytoin concentration of about 40% (21). This interaction is probably due to both drugs competing for hydroxylation via liver microsomal enzymes.
<b>Fluconazole/phenytoin (63)</b>	The broad spectrum antifungal agent, fluconazole, has been implicated in six cases of increased phenytoin serum concentrations and systemic toxicity when the two agents are used together (63). Fluconazole, as with the related ketoconazole, inhibits hepatic oxidative drug metabolizing activities and thus potentiates the action and toxicity of co-administered phenytoin. The onset of toxicity usually occurs within 2–7 days after the start of fluconazole.
<b>Disulfiram/phenytoin (26–28)</b>	It is known that the use of disulfiram in epileptic patients controlled on phenytoin causes a marked rise in serum phenytoin concentrations and may evoke phenytoin overdosage (26, 27). The kinetics of this interaction have been analysed (28) and they indicate that disulfiram affects the elimination rate of phenytoin by non-competitive mechanisms.
<b>Oral contraceptives/phenytoin (37)</b>	<p>Steady-state plasma phenytoin concentrations in 40 oral contraceptive users were higher relative to phenytoin dose than in 135 age-matched non-users of oral contraceptives.</p> <p>This combination is not recommended since the oral contraceptive agents may induce phenytoin toxicity. Also the efficacy of the oral contraceptive is impaired in epileptic patients taking phenytoin due to P450 induction.</p>
<b>Thioridazine/phenytoin (45)</b>	Clinically significant phenytoin intoxication occurred in two cases during concomitant administration of thioridazine. Both drugs are metabolized in the liver

*Combination**Interaction*

**Thioridazine/phenytoin**  
*cont.* and each competes with the other for cytochrome P450 hydroxylation; thus the enzyme system becomes saturated and phenytoin metabolism is inhibited.

## 2. Drugs which Decrease the Effects of Phenytoin

**Alcohol** (64)

**Antacids** (65)

\***Cancer chemotherapy** (66)

bleomycin

cisplatin

vinblastine

**Carbamazepine** (67–68)

\***Dichloralphenazone** (69)

**Phenobarbitone** (70)

**Sodium valproate** (71–73)

These drugs have been reported, sometimes in single or isolated cases (\*) to decrease the effects of phenytoin and adversely affect the control of epilepsy. They interact with phenytoin by a number of mechanisms including liver enzyme induction, decreased absorption of phenytoin from the gut, or even (with cancer chemotherapy) due to intestinal mucosal damage and subsequent reduced absorption. Details of some of the interactions in this category are given below. See also review articles on drug interactions with phenytoin (50, 51).

*Combination**Interaction*

**Alcohol/phenytoin**  
(64, 74) Alcohol induces liver microsomal enzymes and thus increases the metabolism of phenytoin.

**Antacids/phenytoin** (65) Studies in normal subjects showed that, although no specific interaction could be identified, a trend of decreased absorption of phenytoin in the presence of the proprietary antacid Asilone was seen, and in some subjects this decrease was substantial. Concomitant dosage with Asilone or its constituents (dimethicone, aluminium hydroxide gel, light magnesium oxide) may change phenytoin absorption.  
Spacing of dosage of phenytoin and antacid by 3–4 hr should be considered as a precaution.

**Carbamazepine/phenytoin** (67–68) Carbamazepine induces liver microsomal enzymes and thus increases the metabolism of phenytoin.

*Combination**Interaction*

Carbamazepine is also an anti-epileptic agent, and if both drugs are used the patient should be monitored to determine whether adjustment of phenytoin dosage is required.

**Ciprofloxacin/phenytoin  
(75)**

A 78-year-old patient was stabilized on phenytoin 300 mg daily for a history of seizure disorders. Subsequently, he developed a lower lobe abscess on his left lung and was treated with intravenous ciprofloxacin 400 mg per 12h. The plasma phenytoin concentration fell dramatically despite increase in the dose of phenytoin. When ciprofloxacin treatment was stopped the phenytoin plasma concentrations rose to pre-ciprofloxacin levels (75). Changes in plasma concentration of phenytoin when administered concurrently with ciprofloxacin have been anticipated by the manufacturer (Miles Inc, package insert) but this is the first published report of such an interaction. The mechanism involved was thought to be ciprofloxacin's induction of the P450 oxidative enzymes responsible for phenytoin's metabolism.

**Dichloralphenazone/  
phenytoin (69)**

Nightly administration of dichloralphenazone significantly increased the clearance of phenytoin in an epileptic patient due to induced microsomal enzyme activity with loss of epileptic control. The interaction has been confirmed in healthy subjects.

**Phenobarbitone/phenytoin  
(70)**

Phenobarbitone induces liver microsomal enzymes and thus increases the metabolism of phenytoin. The level of phenytoin in the plasma is then reduced to below that attained when phenytoin is given alone. This alteration in phenytoin metabolism does not seem to be a problem in the management of the epileptic patient since phenobarbitone also possesses anticonvulsant activity.

**Valproate/phenytoin  
(71-73)**

Total serum phenytoin concentrations in six epileptic patients were significantly lowered in the presence of valproic acid, but protein binding of phenytoin was reduced to a similar degree so there was no change in calculated concentration of unbound phenytoin (71).

<i>Combination</i>	<i>Interaction</i>
<b>Valproate/phenytoin</b> <i>cont.</i>	Distribution and elimination kinetics of phenytoin in normal subjects confirm these findings (72). The interaction may, however, complicate plasma level monitoring of phenytoin in patients (73). Withdrawal of sodium valproate from a stabilized regimen may result in rise of serum phenytoin to toxic levels.
<b>Verapamil/phenytoin</b> (76-78)	A patient who had taken phenytoin (100 mg twice daily) for presumed epilepsy for 10 years, presented with hypertrophic obstructive cardiomyopathy with dyspnoea and episodes of syncope. Verapamil was started (80 mg twice daily per day rising to 160 mg thrice daily after 17 months). Despite these increases in verapamil dosage her plasma concentration of verapamil remained subnormal and her obstructive cardiomyopathy showed no substantial improvement. When phenytoin treatment was discontinued the plasma concentration of verapamil rapidly rose to expected levels and her condition improved. It was concluded that phenytoin had markedly induced the hepatic metabolism of verapamil and thus markedly reduced the steady-state concentrations of the drug in this patient (76). Other cases have experienced a marked reduction in the steady-state concentrations of verapamil during combined treatment with rifampicin and phenobarbitone (77-78) which are also potent hepatic enzyme inducers.

### 3. Drug Actions Modified by Phenytoin

- Corticosteroids** (20, 79, 80)
  - dexamethasone (20, 79, 80)
  - prednisone (79, 80)
- \*Disopyramide** (81, 82)
- Doxycycline** (83, 84)
- \*Lithium** (35)
- Methadone** (85)
- Mexiletine** (86)
- Mianserin** (87)
- \*Oestrogens** (88)
- Oral contraceptives** (89, 90, 91)
- Pethidine** (meperidine) (92)

**Primidone (93)****Sodium valproate (94)****Theophylline (95–98)**

The therapeutic or toxic effects of the above drugs may be modified in the presence of concomitantly administered phenytoin; there are various mechanisms of action but induction of liver microsomal enzymes by phenytoin is probably the most common. Details of some interactions, which may be single or isolated cases (\*), are given below. See review articles on drug interactions with phenytoin (50, 51).

<i>Combination</i>	<i>Interaction</i>
<b>Corticosteroids/phenytoin</b> dexamethasone (20, 79, 80) prednisone (79, 80)	Phenytoin increases the rate of dexamethasone metabolism with resultant lack of efficacy of this corticosteroid. There is some evidence that prednisone metabolism is less affected by phenytoin-induced enzyme induction.
	Corticosteroids may have a role in the control of some forms of epilepsy. This interaction may therefore have major significance since the expected efficacy of the steroid may not be achieved.
<b>Cyclosporin/phenytoin</b> (99)	Following the clinical observation that patients receiving phenytoin required increased doses of cyclosporin to maintain therapeutic concentrations, the effect of 10 daily doses of phenytoin, sufficient to maintain therapeutic concentrations on the kinetics of cyclosporin, were studied in six volunteers. Phenytoin reduced the mean area under the concentration-time curve from 10.4 to 5.5 mg/l/hour.
<b>Disopyramide/phenytoin</b> (81, 82)	Phenytoin markedly increased the metabolism of disopyramide in one epileptic patient and in two normal subjects (the effect subsided in 2 weeks after stopping phenytoin). Plasma levels and AUC of disopyramide decreased whilst those of its major metabolite, mono- <i>N</i> -dealkyldisopyramide increased.
	This interaction should be anticipated and the dosage of disopyramide may have to be increased to obtain the required anti-arrhythmic effect.

*Combination**Interaction*

<b>Doxycycline and other tetracyclines/phenytoin</b> (83, 84)	The metabolism of doxycycline is accelerated by both phenytoin and carbamazepine (enzyme inducers). Although this effect has been shown in man with respect to doxycycline it will occur with other tetracyclines.
<b>Lithium/phenytoin</b> (35)	Increase in phenytoin dosage from 300 to 400 mg daily evoked lithium-type toxicity in one patient; symptoms disappeared on stopping lithium but reappeared when lithium was restarted. Change from phenytoin to carbamazepine prevented symptoms. However, in another study the introduction of carbamazepine into an established lithium regimen provoked severe CNS toxicity.
<b>Methadone/phenytoin</b> (85)	Methadone-maintained volunteers experienced moderately severe opiate withdrawal within 3–4 days of beginning phenytoin in therapeutic doses. The area under the methadone plasma concentration-time curve decreased while the ratio of pyrrolidine to metabolite excretion in urine for this area increased. This suggests that phenytoin accelerates methadone metabolism.  These findings have clinical importance if phenytoin has to be added or withdrawn from an epileptic patient who is also an addict maintained on methadone.
<b>Mexiletine/phenytoin</b> (86)	Unexpectedly low plasma concentrations of mexiletine were seen in three patients treated with mexiletine and phenytoin. A subsequent study in six normal subjects given a single oral dose of mexiletine (400 mg) before and after 1 week of phenytoin (300 mg/day) showed that the mean half-life of elimination of mexiletine decreased from 17.2 to 8.4 hr; the mean AUC decreased from 17.67 to 6.21 µg/ml/hr.  This enhanced clearance of mexiletine is likely to be due to hepatic mixed-function oxidase enzyme induction by phenytoin.  This interaction is likely to be of clinical significance

<i>Combination</i>	<i>Interaction</i>
<b>Oestrogens/phenytoin</b> (88)	because of the magnitude of the increase in the clearance of mexiletine.
<b>Oral contraceptives/phenytoin</b> (89–91)	Concomitant use of oral contraceptives (combined-type) and anticonvulsants is known to result in breakthrough bleeding, spotting and, in some cases, pregnancy. It is not generally recognized that the effects of HRT are also diminished due to enhanced breakdown of oestrogen due to phenytoin induced enzyme induction. The replacement effect of 1.25 mg daily of Premarin (conjugated oestrogen) was antagonized by 300 mg phenytoin daily. Hot flushes dramatically increased, levels of gonadotropin increased, and serum levels of oestrogen were depressed.
<b>Pethidine/phenytoin</b> (92)	Phenytoin increased the rate of metabolism of pethidine in normal subjects; the 24-hr AUC of the weakly active metabolite, norpethidine, increased by 53% during phenytoin administration after i.v. pethidine, and by 24.7% after oral pethidine. Pethidine's volume of distribution, renal clearance and protein-binding did not change but renal clearance of norpethidine was four times that of pethidine and was not altered by phenytoin.
	Analgesia is related to pethidine concentration, therefore higher or more frequent doses of pethidine may be required when patients are also on long-term phenytoin.
<b>Primidone/phenytoin</b> (93)	Primidone exerts its anticonvulsant action, at least in part, by its oxidation <i>in vivo</i> to phenobarbitone. The ratio of derived phenobarbitone to unmetabolized primidone was significantly higher in epileptic patients treated with a combination of primidone and phenytoin than in patients on primidone alone. This interaction should not present clinical problems since epileptic patients are stabilized on drug combinations. However, if primidone dosage is altered or if the drug is withdrawn then the dosage of phenytoin will have to be adjusted. It is important with such combined dosage

*Combination**Interaction*

**Primidone/phenytoin  
cont.**

that patient compliance is assured with both components.

**SSRI antidepressants/  
mephenytoin (87)**

The 4'-hydroxylation of *S*-mephenytoin was competitively inhibited by fluoxetine, sertraline, paroxetine and citalopram and their major metabolites *S*-mephenytoin is a representative substrate for the CYP2 C19 subfamily of P450.

**Sodium valproate  
(Epilim)/phenytoin (94)**

Valproate (as acid or sodium salt) may cause drowsiness, stupor or coma when given with other anticonvulsants (phenytoin, carbamazepine, primidone or phenobarbitone). Four cases suggest this is the result of an interaction and not a direct side effect of valproate.

Clinicians should be alert to the possibility that alterations in consciousness can occur when valproate is added to other anticonvulsant regimens.

**Theophylline/phenytoin  
(95–98)**

Pharmacokinetic studies in asthmatic patients and in normal subjects showed that doses of phenytoin that gave plasma concentrations in the therapeutic range decreased the half-life of theophylline (mean, 10.1–5.2 hr) and increased its clearance approximately two-fold. Phenytoin-induced hepatic enzyme induction is the likely mechanism of this interaction (95).

Special attention should be paid to the dosage of theophylline in patients with airway obstruction when drugs with enzyme-inducing activity are introduced or discontinued. Increase in theophylline dosage by a factor of 1.5–2 should be anticipated when phenytoin is added to long-term theophylline therapy.

In a volunteer study, phenytoin (100 mg thrice daily for 3 weeks) significantly reduced the half-life of theophylline (5 mg/kg i.v. as aminophylline) and this was associated with an increase in the rate of theophylline clearance (96). Earlier studies have reported this interaction (97) and it has also been shown that phenytoin absorption is reduced when the

*Combination**Interaction*

two drugs are ingested at the same time (98). The resultant equation of this interaction is that both drugs will show reduced serum concentrations at steady state after multiple doses.

**II. INTERACTIONS WITH PHENOBARBITONE***Combination**Interaction*

<b>Alcohol/phenobarbitone (66)</b>	Enhanced sedative effect.
<b>Antibacterials/phenobarbitone (66)</b>	The metabolism of chloramphenicol, doxycycline, metronidazole are all accelerated and the antibacterial effect is reduced.
<b>Antidepressants/phenobarbitone (66)</b>	Antagonism of anticonvulsive effect of anti-epileptics due to lowering of convulsive threshold by mianserin and tricyclics. Metabolism of mianserin and tricyclics accelerated due to P450 induction by phenobarbitone.
<b>Antifungals/phenobarbitone (66)</b>	Phenobarbitone induces P450 and thus increases griseofulvin metabolism and reduces its efficacy.
<b>Anticoagulants/phenobarbitone (66)</b>	The anticoagulant effect of both warfarin and nicoumalone are reduced due to enzyme induction by phenobarbitone. Bleeding may occur in anticoagulated patients if phenobarbitone is withdrawn.
<b>Calcium channel blockers/phenobarbitone (66)</b>	The effect of diltiazam, felodipine, isradipine, verapamil, nicardipine and nifedipine reduced due to increased metabolic breakdown by phenobarbitone.
<b>Corticosteroids/phenobarbitone (100)</b>	Metabolism of corticosteroids enhanced with loss of clinical efficacy.
<b>Cyclosporin/phenobarbitone (100)</b>	A 4-year-old girl, who was receiving phenobarbitone 50 mg bd and who was administered cyclosporin in a standard fashion sufficient to produce trough levels, remained below the limit of the assay ( $>60$ ng/ml) even after increasing the dose. On reduction of the phenobarbitone dose cyclosporin A levels rose. It

<i>Combination</i>	<i>Interaction</i>
<b>Cyclosporin/ phenobarbitone cont.</b>	appears likely that in man (as has been shown in rats) phenobarbitone induces the cytochrome P450 metabolism of cyclosporin A.
	Phenobarbitone increases the dosage of cyclosporin required to obtain therapeutic levels of the drug.
<b>Dextropropoxyphene/ phenobarbitone (23)</b>	Serum concentrations of phenobarbitone increased by a mean 20% in four epileptic patients after 1 week on dextropropoxyphene (65 mg tid). The clinical significance of this interaction is uncertain but patients receiving this combination should be followed carefully for signs of enhanced barbiturate activity.
<b>Oestrogens/ phenobarbitone (101, 102)</b>	The efficacy of oral contraceptives can be impaired if phenobarbitone is used as an anticonvulsant. The efficacy of hormone replacement therapy (HRT) will also be impaired by phenobarbitone-induced increased rate of metabolism.
<b>Theophylline/ phenobarbitone (66)</b>	The metabolism of theophylline is accelerated and its clinical efficacy reduced.
<b>Thyroxine/ phenobarbitone (66)</b>	The metabolic breakdown of endogenous and exogenous thyroxine is accelerated. Patients whose hypothyroidism has previously been controlled may need an increase in thyroxine dosage if phenobarbitone is administered.
<b>Vitamin D/ phenobarbitone (66, 140)</b>	Increased metabolism of Vitamin D occurs. This is thought to be one of the mechanisms of hip fracture associated with phenobarbitone usage (140).

### III. DRUG INTERACTIONS WITH CARBAMAZEPINE

An analysis of therapeutic failure with carbamazepine revealed that in seven out of 131 cases (5.3%) failure was due to a drug interaction (103). Interacting drugs which will lower the carbamazepine blood level have been listed and include: other anticonvulsant agents (phenytoin, phenobarbital, primidone, valproic acid, progabide) theophylline, isoretinoic, chloramphenicol and cytostatic agents.

Drugs which, if taken concurrently may increase serum carbamazepine levels,

have been listed as: acetazolamide, allopurinol, cimetidine, danazol, desipramine, diltiazem, disulfiram, erythromycin, fluoxetine, isoniazid, josamycin, nicotinamide, phenelzine, propoxyphene, troleandomycin, verapamil and viloxazine.

<i>Combination</i>	<i>Interaction</i>
<b>Antibacterial agents/carbamazepine</b> macrolide antibiotics (66, 104–106) e.g. clarithromycin erythromycin troleandomycin	The evidence from reports suggests that these antibiotics elevate plasma carbamazepine levels by their inhibitory effect on metabolizing microsomal enzyme systems. Combinations of carbamazepine with macrolide antibiotics should be avoided.
isoniazid (107)	Increases in carbamazepine serum concentrations and signs of toxicity have been reported in an 18-year-old female following oral isoniazid (300 mg/day) for 5 days. Carefully monitor patients on this combination; reduction in carbamazepine dosage should be anticipated.
tetracyclines (66)	Patients should be monitored for effective antibiotic activity if doxycycline (or other tetracyclines) is given in combination with phenytoin, carbamazepine or other known enzyme inducer. It may be necessary to avoid this particular combination.
<b>Anticoagulants/ carbamazepine</b> (66)	The metabolism of warfarin and nicoumalone are accelerated, i.e. reduced anticoagulant effect when given with carbamazepine.
<b>Antidepressants/ carbamazepine</b> (23, 66)	Antagonism of anticonvulsant effect by tricyclic antidepressants and mianserin. Carbamazepine should not be administered with or within 2 weeks of discontinuing of MAOI therapy. Plasma concentrations of carbamazepine are increased by the SSRIs i.e. fluoxetine, fluvoxamine and viloxazine.

*Combination**Interaction*

<b>Calcium antagonists/ carbamazepine (108–109)</b> e.g. verapamil diltiazem nifedipine	<p>It has been suggested that calcium antagonists, such as verapamil and diltiazem, might be effective adjuncts to anticonvulsant therapy by inhibiting the propagation of seizures (108). A 34-year-old man was treated (109) with carbamazepine for epilepsy for 1 year. Verapamil was then added to the regime since he continued to have seizures 4 times/day. He developed signs of carbamazepine toxicity (12–13 mg/l). After 3 months the patient was tried on nifedipine as the calcium antagonist. No signs of carbamazepine toxicity occurred.</p> <p>Diltiazem and verapamil inhibit hepatic monooxygenase activity in mice by binding to cytochrome P450. Nifedipine belongs to a group of calcium antagonists (dihydropyridines) which is structurally different from diltiazem and verapamil. The authors (99) believe that calcium antagonist therapy with nifedipine and carbamazepine is satisfactory but not with other agents.</p>
<b>Plastic nasogastric tubes/carbamazepine (113–115)</b>	<p>Significant losses of carbamazepine has been reported after a suspension of the drug was administered via polyvinyl nasogastric feeding tubes. Losses of up to 23% were recorded. The drug is thought to 'sorb' to the plastics material (113). This may be alleviated by mixing the suspension with an equal volume of diluent before administering the suspension. A similar problem has arisen with the administration of phenytoin by this route (114). Another study involving nasogastric feeding has found reduced activity of administered phenytoin which was attributed to phenytoin being bound to the enteral feed components (115).</p>
<b>Terfenadine/ carbamazepine (116)</b>	<p>An 18-year-old woman suffered an interaction between the antihistaminic terfenadine and carbamazepine which resulted in her hospitalization. She presented with symptoms of confusion, disorientation and visual hallucinations, nausea and ataxia which had developed</p>

<i>Combination</i>	<i>Interaction</i>
	shortly after taking terfenadine 60 mg twice daily by mouth for the symptomatic relief of rhinitis. On admission her serum levels of total carbamazepine were within normal limits but her serum levels of free carbamazepine were almost three times the upper limit of normal. Because terfenadine and carbamazepine are both highly protein bound, it was thought that terfenadine had displaced the carbamazepine, resulting in higher than normal free carbamazepine levels. Treatment with terfenadine was stopped and the patient's free carbamazepine serum levels fell to normal with a corresponding resolution of her toxic symptoms (116).
<b>Cimetidine/ carbamazepine</b> (110, 111)	Eleven epileptic patients taking regular carbamazepine or carbamazepine and phenytoin were treated with cimetidine 300 mg tds for 7 or 10 days (110). No change in carbamazepine steady-state plasma levels was observed. A mean rise in phenytoin levels of 28% was found by 1 week.
	Cimetidine (400 mg daily) caused increased plasma carbamazepine concentrations and neurological toxicity in an elderly woman who had been successfully treated with carbamazepine (600 mg daily) for 20 years for trigeminal neuralgia (111).
<b>Dextropropoxyphene/ carbamazepine</b> (23, 112)	Dextropropoxyphene added to regular carbamazepine regimen (alone or with phenobarbitone) produced severe side effects and 45–77% increase in plasma concentrations of carbamazepine in seven patients (112). In another study, the serum concentrations of carbamazepine increased by a mean of 66% in six epileptic patients after 5 days on dextropropoxyphene (65 mg tid). This level was maintained or increased during a further week's treatment with dextropropoxyphene and one patient showed signs of clinical toxicity (23).
<b>Lithium/carbamazepine</b> (23)	The combination of lithium and carbamazepine may cause enhanced lithium toxicity despite lithium plasma concentrations being within the therapeutic range.

**IV. DRUG INTERACTIONS WITH SODIUM VALPROATE**

<i>Combination</i>	<i>Interaction</i>
<b>Valproic acid/antacids (117)</b>	A limited study in seven normal subjects indicated that three commonly prescribed antacids (Maalox, Trisogel and Titralac), particularly aluminium and magnesium hydroxide suspension (Maalox), may increase the bioavailability of oral doses of valproic acid. The clinical significance of this finding at steady-state levels of valproic acid, has yet to be established but caution should be exercised if valproic acid and antacids are administered concurrently.
<b>Valproic acid/aspirin (118, 119)</b>	In five of six epileptic children taking 18–49 mg/kg daily valproic acid (VPA), the steady-state serum-free fractions of VPA rose from 12 to 43% when antipyretic doses of aspirin were taken (118). Mean total VPA half-life rose from 10.4 to 12.9 hr and mean free VPA half-life rose from 6.7 to 8.9 hr when salicylate was present in the serum. Salicylate appeared to displace VPA from serum albumin <i>in vivo</i> , but increased VPA half-life and changes in VPA elimination patterns suggested that serum salicylate also altered VPA metabolism. A related study, also in children, showed that aspirin (up to 68 mg/kg daily) caused decreased clearance of free fraction and 49% increased free serum levels of valproate. It was concluded that co-administration of these drugs for more than 24 hr might result in toxic levels of valproic acid due to competition for active transport sites in renal tubules or liver.
<b>Sodium valproate/ diazepam (120, 121)</b>	Although no untoward effects were reported in these studies, the results strongly suggest that prolonged use of salicylates in combination with valproic acid may result in greater than anticipated free serum levels of VPA with cumulation to toxic levels.
	Serum protein binding of diazepam is competitively inhibited by valproic acid (from 98.1 to 96.1%) (120). In another study, oral sodium valproate (1500 mg/day) displaced diazepam from protein binding sites (unbound fraction in serum increased two-fold) and

<i>Combination</i>	<i>Interaction</i>
	<p>inhibited its metabolism in a kinetic study in normal subjects (121).</p> <p>This interaction may have clinical implications since diazepam is frequently used in epileptic patients for its anticonvulsive effect, or in the treatment of co-existing anxiety or spasticity.</p>
<b>Valproic acid/phenobarbitone (122-125)</b>	<p>The mean half-life of phenobarbitone acid in six normal subjects increased from 96 to 142 hr after taking valproic acid (250 mg bid) for 14 days. Plasma clearance of phenobarbitone fell from 4.2 to 3.0 ml/hr/kg; renal clearance did not change; the metabolic clearance fell from 3.3 to 2.0 mg/hr/kg. More of the phenobarbitone was excreted unchanged and the fraction metabolized fell from 0.78 to 0.67. This suggests that valproic acid inhibits the metabolism of phenobarbitone (122). It has been shown that valproate inhibits the direct <i>N</i>-glucosidation of phenobarbitone and the <i>O</i>-glucuronation of <i>p</i>-hydroxy phenobarbitone (122).</p> <p>Of 13 patients with complex partial seizures who experienced stuporous states during treatment with sodium valproate (SVP), four received SVP only, four received SVP and phenobarbitone (PB), and five received SVP, PB and a third commonly used anticonvulsant (carbamazepine, clonazepam, diazepam or phenytoin). Stupor therefore seemed to be related to an intrinsic effect of SVP which was sometimes potentiated by other anticonvulsants. EEG symptoms observed during SVP-induced episodes resembled those of spontaneously occurring partial seizures (123-124).</p> <p>Clinicians should be alert to the possibility that alterations in consciousness can occur when valproate is added to other anticonvulsant regimens.</p> <p>Hyperammonaemia and hepatotoxicity have also been reported to increase in frequency when valproate is used in combination with other anti-epileptic drugs (125).</p>

## V. INTERACTIONS WITH THE NEWER ANTIEPILEPTIC AGENTS (GABAPENTIN, LAMOTRIGINE, VIGABATRIN)

Little is known of the clinical interactions with the new anti-epileptics, but all current information (126–133) would indicate that they are freer from adverse interactions than the older and currently well established agents.

<i>Combination</i>	<i>Interaction</i>
<b>Antacids/gabapentin (126)</b>	Magnesium and aluminium salts slightly reduce the absorption of gabapentin.
<b>Cimetidine/gabapentin (130–131)</b>	Cimetidine has been reported to slow the clearance of gabapentin.
<b>Anti-epileptic agents/lamotrigine (126)</b>	Enzyme-inducing anti-epileptic drugs, carbamazepine, phenobarbitone, phenytoin and primidone, increase the elimination of lamotrigine shortening its normal 24-hr half-life to 15 hr. Efficacy of lamotrigine is reduced.
<b>Sodium valproate/ lamotrigine (132, 133)</b>	Sodium valproate inhibits the metabolism of lamotrigine lengthening its half-life to as much as 60 hr. In those patients taking sodium valproate the dose of lamotrigine is 25 mg alternate days for the first 2 weeks, followed by 25 mg once a day for 2 weeks. Thereafter the usual dose of 100–200 mg/day may be given.
<b>Phenytoin/vigabatrin (129, 132)</b>	Vigabatrin slightly lowers (20%) phenytoin levels by an undetermined mechanism.
<b>Felbamate/other anti-epileptic agents (136–140)</b>	Felbamate reduces the clearance of agents phenytoin, phenobarbitone and valproate and increases the clearance of carbamazepine. Its own metabolic clearance is increased by phenytoin, carbamazepine

*Combination**Interaction*

and phenobarbitone (135–139). There is no clinically relevant interaction between vigabatrin and felbamate (139).

**VI. DRUGS WHICH INCREASE THE RISK OF EPILEPTIFORM SEIZURES****Oral contraceptives** (89, 142)**Reserpine** (143)**Rifampicin** (144)**Tricyclic antidepressants** (65–68)

These drugs have been reported to increase the risk of epileptiform seizures; indeed tricyclic antidepressants can produce grand mal fits in non-epileptic patients. The interactions within this group are more related to drug–disease interaction than to the drug–drug variety. Details of some of the interactions in this category are given below.

*Combination**Interaction***Oral contraceptives**  
(89, 142)

Oral contraceptives (combined type) may cause fluid retention which may precipitate seizures in epileptics. Cases of oral contraceptive-induced exacerbation of epilepsy have been reported. Phenytoin may reduce the efficacy of oral contraceptives due to enzyme induction. The use of this combination has to be carefully assessed with respect to possible failure of contraception and due, in some cases, to increased incidence of fits. Where possible, it would be better to advise alternative methods of contraception.

**Reserpine** (143)

Reserpine lowers the convulsive threshold; anticonvulsant dosage may have to be adjusted to control epilepsy. Although severe problems have not been reported, reserpine should be used with caution in epileptic patients controlled on anticonvulsants; the necessity for increasing the dose of anticonvulsant should be anticipated.

**Rifampicin/isoniazid  
and ethambutol** (144)

Rifampicin increases the clearance of phenytoin by two-fold. This effect is not ameliorated by the

*Combination**Interaction***Rifampicin/isoniazid and ethambutol cont.**

addition of other standard anti-TB therapy: isoniazid and ethambutol.

Rifampicin alone or in combination with other anti-TB drugs significantly reduces the effect of phenytoin.

**Tricyclic antidepressants (145–148)**

Tricyclic antidepressants (e.g. amitriptyline, imipramine) may produce epileptiform seizures in susceptible patients. High doses can produce grand mal fits even in non-epileptic patients (148).

Caution should be observed if tricyclic antidepressants are given to patients with epilepsy. Patients should be carefully supervised during such treatment, and the necessity for increasing the anticonvulsant dosage should be anticipated.

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## **4.5 INTERACTIONS WITH DRUGS USED IN THE TREATMENT OF PARKINSONISM**

Three main pharmacological classes of drug are used in the treatment of parkinsonism (1).

### **I. DOPAMINERGIC AGENTS**

In idiopathic parkinsonism, progressive degeneration of the pigmented cells of the substantia nigra are associated with a deficiency of the neurotransmitter dopamine. The pathogenesis of this is obscure and therapy with dopaminergic agents is simply an attempt to correct the neurohumoral imbalance.

#### **1. Levodopa**

Levodopa used with a dopa-decarboxylase inhibitor is the treatment of choice for patients with disabling idiopathic Parkinson's disease. Levodopa is the amino acid precursor of dopamine, and acts by replenishing the depleted striatal dopamine. Levodopa has a greater effect on bradykinesia and rigidity than on parkinsonian tremor.

Levodopa is usually administered with an extra-cerebral dopa-decarboxylase inhibitor which prevents the peripheral degradation of levodopa to dopamine. Dopamine unlike levodopa does not cross the blood-brain barrier. By preventing the peripheral degradation of levodopa, higher effective levels of levodopa reach the brain where it is converted to dopamine. At the same time, since lower doses of levodopa can be administered, the peripheral side effects of levodopa which are principally nausea, vomiting, etc., are reduced. There is also less delay in the onset of clinical response to treatment. An increased incidence of abnormal involuntary movements especially of mouth, jaw and tongue is a disadvantage of the use of peripheral dopa-decarboxylase inhibitors.

The extra-cerebral dopa-decarboxylase inhibitors in clinical use are given in fixed combinations with levodopa. Benserazide is given in a fixed ratio of 1 part benserazide with 4 parts levodopa by weight, and the combination is known as co-beneldopa. Carbidopa is given with levodopa in ratios of either 1 part carbidopa to 10 parts levodopa or 1 part carbidopa to 4 parts levodopa, irrespective of the ratio the two agents in combination is known as co-careldopa. The fact that two different ratios exist under the same British Approved Name (BAN) (1) is a serious risk factor and

is yet another reason why the British Pharmacopoeia's introduction of co-names for combination products is to be condemned on safety grounds.

Improvement of parkinsonism with levodopa may occur over 6–18 months and such improvement may be sustained for up to 2 years. Particularly troublesome to patients is the 'on–off' effect which is characterized by fluctuations of performance during the 'on' period and incapacitating weakness and akinesia during the 'off' periods which may last up to 4 hr. The 'on–off' effect increases in frequency as duration of treatment increases.

## **2. Selegiline (16)**

Selegiline is a monoamine oxidase-B inhibitor which may be used in early treatment of parkinsonism or in patients on levodopa to smooth the symptoms of the 'on–off' effect. Selegiline inhibits the breakdown of dopamine in the brain. It also inhibits the re-uptake of dopamine at the presynaptic dopamine receptors. These effects potentiate dopaminergic function in the brain and help to prolong the effect of both endogenous and exogenous dopamine. Unlike conventional MAO inhibitors, which inhibit both MAO-A and MAO-B enzyme, the selectivity of selegiline for the MAO-B enzyme means it can be safely given with levodopa without risk of a hypertensive crisis. Selegiline may be administered with levodopa alone or in combination with a peripheral dopa-decarboxylase inhibitor. Similarly there are no dietary restrictions with selegiline and tyramine containing foods.

## **3. Apomorphine (17)**

Apomorphine is a potent dopamine agonist for both D<sub>1</sub> and D<sub>2</sub> receptors and is used for refractory motor fluctuations in Parkinson's disease, i.e. 'on–off' episodes. Apomorphine has an onset of action following subcutaneous injection of 5–10 min and may prevent or terminate an 'off' episode. Side effects associated with apomorphine are emesis, nausea, retching, yawning and sedation.

## **4. Dopaminergic Agents, e.g. Bromocriptine (19), Lysuride (20), Pergolide (21)**

These are all thought to work by direct stimulation of surviving dopamine receptors. All these dopaminergic drugs may cause serious neuropsychiatric side effects and have been reported to cause retroperitoneal fibrosis (1, 19).

## **5. Amantidine (17)**

Amantidine has a modest effect on bradykinetic disabilities as well as on tremor and rigidity. Unfortunately relatively few patients experience benefits from this agent, which started its clinical use as an antiviral, and is relatively free of adverse effects.

## II. ANTIMUSCARINIC DRUGS USED IN PARKINSONISM

Antimuscarinic drugs exert their effect by correcting the relative excess of cholinergic effects which occurs as a result of dopamine deficiency. They are less effective than levodopa in Parkinson's disease but may be a useful supplement to therapy. In most patients their effect is only moderate and limited to a reduction of tremor and rigidity without effect on bradykinesia. The most commonly used antimuscarinic agents are:

**benzhexol hydrochloride**  
**benztropine mesylate**  
**biperiden**  
**orphenadrine hydrochloride**  
**procyclidine hydrochloride**

No important differences exist between these drugs but patients may find one or other suits them better. It has been claimed that this group has a greater therapeutic effect in post-encephalitic parkinsonism than in idiopathic parkinsonism. Tardive dyskinesia is not improved by antimuscarinic agents and may in fact be made worse.

## III. DRUG USED TO CONTROL TREMOR

A variety of agents (1) have been tried to control tremor. **Tetrabenazine** acts by depleting nerve endings of dopamine. Other agents used have included **benzhexol**, **haloperidol**, **pimozide**, **sulpiride**,  **$\beta$ -adrenergic blocking agents**, **primidone**, and **piracetam**.

### *Combination*

### *Interaction*

#### **LEVODOPA**

**Antidepressant/levodopa**  
 (MAOI or tricyclic)

The combination of a MAOI and an amine precursor, such as levodopa, is potentially dangerous as it may evoke a hypertensive crisis due to increased storage and release of either dopamine or noradrenaline, or both (2, 3). In contrast, it had been thought that the tricyclic antidepressants imipramine and amitriptyline could be given to patients taking levodopa without fear of a harmful pressor effect (3). However, a hypertensive crisis has been observed following the administration of co-careldopa (Sinemet) and metoclopramide to a patient on amitriptyline (4), and this interaction has been confirmed by the reports of similar adverse responses (5). It has been suggested

<i>Combination</i>	<i>Interaction</i>
<b>Antidepressant/levodopa cont.</b>	that the effect of biogenic amines in the CNS is potentiated by tricyclic antidepressants via the blockade of their major route of physiological inactivation, i.e. the re-uptake by the presynaptic nerve terminals.
	MAOIs and levodopa should not be given concomitantly, nor within 2 weeks of stopping treatment with a MAOI drug. If necessary, the treatment recommended for this interaction is the use of a short acting $\alpha$ -adrenergic blocking agent, for example phentolamine. It is also now apparent that levodopa can enter into potentially dangerous interactions with tricyclic antidepressants also leading to a hypertensive crisis. Treatment of this is as described for MAOIs.
<b>Antihypertensive agent/levodopa (6)</b>	Levodopa potentiates the hypotensive effects of guanethidine and reserpine-containing preparations; the CNS-depressant actions of reserpine are also enhanced. Reserpine may cause parkinsonism in its own right since it induces dopamine depletion in the brain, which is in direct opposition to the action of levodopa in relieving parkinsonism. Reserpine therefore antagonizes levodopa (7, 8). Methyldopa may also diminish the effects of levodopa in parkinsonism, but together they have enhanced hypotensive effects; although severe hypotension has not been reported (9, 10).
<b><math>\beta</math>-Adrenergic blocking drug/levodopa (11)</b>	The effects of combined therapy with levodopa and propranolol were studied in 25 parkinsonian patients in whom tremor was a dominant clinical feature. When the drugs were given together tremor was rapidly reduced or abolished in all except two patients who had undergone thalamotomy. Improvement was sustained during follow-up periods ranging from 6 months to 2 years. Not less than 60 mg of propranolol were administered daily in three or four divided doses. The action of propranolol is thought to be directly on the tremorigenic neurohumoral system. There is experimental evidence to suggest that

<i>Combination</i>	<i>Interaction</i>
	propranolol exerts a central action on the reticular formation independently of the metabolism of catecholamines (12). This effect is probably common to all $\beta$ -adrenergic blockers which cross the blood-brain barrier. (Practolol which does not cross the blood-brain barrier had no such effect.)
<b>Benzodiazepines/levodopa</b>	Levodopa antagonizes the effects of chlordiazepoxide diazepam, lorazepam (1, 6, 13–15). A parkinsonian patient, stabilized successfully with levodopa (500 mg six times daily), who experienced a marked reduction in response to levodopa after taking chlordiazepoxide (10 mg tid) for 2 weeks. Her Parkinsonism worsened and she had coarse tremor and rigidity and could not walk straight. Five days after chlordiazepoxide was stopped, her Parkinson's disease was again well controlled. The mechanism of this interaction is not known.
<b>Isoniazid/levodopa</b> (16)	Some evidence has been presented to suggest that isoniazid and levodopa may interact to produce a hypertensive reaction similar to that produced by the cheese–isoniazid interaction (17), which is itself similar to the established MAOI–cheese interaction.
<b>Pyridoxine (vitamin B<sub>6</sub>)/levodopa</b> (18)	Pyridoxine reduces the effect of levodopa in the treatment of parkinsonism. Pyridoxine is a co-decarboxylase and by facilitating the decarboxylation of levodopa it reduces its blood level. Pyridoxine is commonly included in multivitamin preparations. Pyridoxine and pyridoxine-containing formulations should not be given to patients on levodopa therapy.
<b>Selegiline/levodopa</b> (19)	Selegiline does not alter the distribution or elimination of levodopa in young healthy male volunteers.
<b>Tranquillizer/levodopa</b> e.g. phenothiazines (20, 21) butyrophenones (8) thioxanthenes (8)	All three groups of tranquillizers interfere with central amine mechanisms; combinations with levodopa should therefore be avoided where possible. Phenothiazines may reduce the effects of levodopa.

*Combination**Interaction***Tranquillizer/levodopa  
cont.**

*Phenothiazines can cause parkinsonism in their own right.*

Avoid these combinations where possible. If, however, the combined administration is considered essential, extreme care should be exercised and a close watch kept for any signs of potentiation, antagonism of other interactions and for any unusual side effects. It should also be noted that some antihistamines are phenothiazine derivatives (e.g. promethazine, dimethothiazine, methdilazine, trimeprazine) and might therefore be expected to diminish the effects of levodopa if given concomitantly.

**SELEGILLINE****Levodopa/selegiline  
(19, 22–25)**

Selegiline does not alter the distribution of levodopa or its elimination in healthy young male volunteers. A major study conducted on behalf of the Parkinson's Disease Research Group of the United Kingdom (23) found a 60% increase in mortality in 271 patients with early mild Parkinson's disease treated with selegiline plus levodopa (76 deaths, 28.0% mortality) compared with 249 patients treated with levodopa alone (44 deaths, 17.7% mortality) in the study period. Parkinson's disease is not usually associated with a high mortality in its early stages and the mortality in both groups in this study was very high. No reasonable explanation for these findings were advanced. The results of this study (23) is at variance with the findings of other workers (24, 25). Maki-Ikola *et al.* (24) found a 2.8% mortality over 3.5 years in 936 patients treated with levodopa plus selegiline for Parkinson's disease compared with a 3.3% mortality in the same period in 1093 patients treated with levodopa alone or placebo. Olanow and Godbold (25) found a 10% mortality in a group of 50 patients with Parkinson's disease who had not received selegiline compared with a 5.9% mortality in a group of 51 patients who had received selegiline.

**MAOI/selegiline (22)**

Selegiline should not be given with non-selective MAOI inhibitors.

<i>Combination</i>	<i>Interaction</i>
<b>Pethidine/selegiline (22)</b>	Hyperpyrexia and CNS effects have been reported.
<b>SSRIs</b> <b>fluoxetine/selegiline (22)</b>	Hypertension and CNS excitation have been reported with fluoxetine, but this could be a general reaction with all SSRIs.
<b>APOMORPHINE</b>	
<b>Antipsychotic agents/ apomorphine</b> e.g. phenothiazines (1, 26)	Apomorphine antagonizes the effects of antipsychotic agents. Apomorphine can lead to neuropsychiatric disturbances itself and should not be given to patients with pre-existing psychiatric problems, or dementias due to other pathological problems.
<b>AMANTIDINE</b>	
<b>Antihypertensives</b> <b>methyldopa/amantidine</b>	Increased risk of extrapyramidal side effects (1, 27).
<b>Antipsychotics</b> <b>phenothiazines/amantidine</b>	
<b>Metoclopramide/amantidine</b>	
<b>Tetrabenazine/amantidine</b>	
<b>DOPAMINERGIC AGENTS: e.g. BROMOCRIPTINE (19), LYSURIDE (20) AND PERGOLIDE (21)</b>	
<b>Alcohol/dopaminergic agents (28–30)</b>	Alcohol reduces bromocriptine tolerance.
<b>Antibiotics/dopaminergic agents (28–30)</b> e.g. erythromycin	Erythromycin increases bromocriptine plasma levels and increases toxicity.
<b>Antipsychotic drugs/ dopaminergic agents (28–30)</b>	Bromocriptine, lysuride and pergolide antagonize the therapeutic action of the major antipsychotic agents. Antipsychotic agents, such as phenothiazines butyrophenones, thioxanthines, haloperidol and

<i>Combination</i>	<i>Interaction</i>
<b>Antipsychotic drugs/ dopaminergic agents</b> <i>cont.</i>	sulpiride, antagonize the antiparkinson and hypoprolactinaemic actions of bromocriptine.
<b>Metoclopramide/ dopaminergic agents</b> (28–30)	Metoclopramide antagonizes the effectiveness of bromocriptine and pergolide.

## ANTIMUSCARINIC AGENTS

<b>Antidepressants/</b> <b>Antimuscarinic agents</b> e.g. monoamine oxidase inhibitors and tricyclic antidepressants (1, 31)	MAOIs interact with antimuscarinic agents and cause dry mouth, blurred vision, urinary hesitancy, urinary retention and constipation. Tricyclic antidepressants can similarly interact, but have additionally been reported to cause glaucoma and paralytic ileus.
<b>Antiarrhythmics/</b> <b>Antimuscarinic agents</b> (1, 31)	Disopyramide causes increased antimuscarinic side effects.
	Antimuscarinic agents delay the absorption of mexiletine.
<b>Antifungals/</b> <b>Antimuscarinic agents</b> (1, 31)	Antimuscarinics delay the absorption of ketoconazole.
<b>Sublingual nitrate tablets/antimuscarinic agents (1, 31)</b>	Reduced effect of sublingual nitrate tablets due to dry mouth causing failure to dissolve under the tongue.

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# CHAPTER 5

## Drug Interactions with Antimicrobial Agents

The variety of chemical families represented as having antibacterial, antifungal or antiviral activities are legion. In this chapter the families of compounds with clinical antibacterial actions are presented alphabetically (15 such families potential for interactions with other drugs *in vivo* are reviewed). The antituberculous, antifungal and antiviral agents are presented by therapeutic activity.

### 5.1. AMINOGLYCOSIDES

INN approved name:

Amikacin	Neomycin
*Capreomycin	Netilmicin
Gentamicin	*Streptomycin
Kanamycin	Tobramycin

\*Used as antituberculous agents.

The major adverse effects of this group of antibiotics are nephrotoxicity and ototoxicity. The risk of ototoxicity is enhanced if two aminoglycoside antibiotics are co-administered; the risk of nephrotoxicity is increased if an aminoglycoside antibiotic is administered with a polypeptide such as colistin or systemic antifungal agents such as amphotericin B or the glycopeptide antibiotics, vancomycin or telcoplanin, and cisplatin (see reviews by Barclay and Begg (1994), Begg and Barclay (1995) and Duffnell and Begg (1994), for publication details, see Recommended further reading section).

<i>Combination</i>	<i>Interaction</i>
<b>Bisphosphonates/ aminoglycoside antibiotics (1–4)</b> e.g. disodium etidronate disodium pamidronate disodium clodronate	Co-administration of aminoglycoside antibiotics with bisphosphonates can lead to severe hypocalcaemia. Aminoglycosides and bisphosphonates can induce hypocalcaemia by different mechanisms, these effects can summate. The warning about interactions between bisphosphonates and aminoglycoside antibiotics is given in the British National formulary (1) but not in the relevant bisphosphonate data sheets of the ABPI Data Sheet Compendium 1995–96 (2–4).
<b>Cephalosporins/ aminoglycoside antibiotics (5)</b>	The potential nephrotoxicity of cephalosporins may be increased by gentamicin.
<b>Cholinergic agents/aminoglycoside antibiotics (1)</b> e.g. neostigmine physostigmine distigmine bromide pyridostigmine bromide	Aminoglycosides can antagonize the effects of cholinergic agents, such as neostigmine used in myasthenia gravis or physostigmine used as eyedrops for glaucoma.
<b>Cisplatin/aminoglycoside antibiotics (1)</b>	Increased risk of both nephrotoxicity and ototoxicity when cisplatin is used at the same time as an aminoglycoside antibiotic.
<b>Digoxin/aminoglycoside antibiotics (18)</b>	Neomycin impairs the absorption of digoxin.
<b>Diuretics/aminoglycoside antibiotics e.g. ethacrynic acid frusemide (1, 5–10)</b>	Increased risk of ototoxicity if loop diuretics are used with aminoglycoside antibiotics (also with colistin and vancomycin).
<b>Heparin/aminoglycoside antibiotics (32–34)</b>	Aminoglycoside activity is inhibited by heparin. Tobramycin, gentamicin and netilmicin are all affected by heparin.
<b>Muscle relaxants/aminoglycoside antibiotics</b>	Aminoglycosides potentiate the effects of non-depolarizing muscle relaxants such as tubocurarine.

<i>Combination</i>	<i>Interaction</i>
e.g. decamethonium succinylcholine tubocurarine (1, 5, 10-12, 18-29)	Kanamycin, neomycin, tobramycin, viomycin and the streptomycins have all been shown to produce neuromuscular blockade and also to potentiate skeletal muscle relaxant drugs. Neomycin, streptomycin and viomycin produce a curare-like blockade. Kanamycin produces a de-polarizing neuromuscular block. Neuromuscular blockade produced by aminoglycosides is enhanced in circumstances of $K^+$ depletion or low ionized $Ca^{2+}$ . Intravenous $Ca^{2+}$ can be useful in reversing blockade but cholinergics such as edrophonium are of little use. These reactions and prolonged respiratory paralysis are more common in patients with myasthenia gravis or Parkinson's disease (19).
<b>Penicillins/aminoglycoside antibiotics</b> (5, 13, 14, 18, 30, 31)	Neomycin has been shown to inhibit the intestinal absorption of penicillin V (phenoxyethyl penicillin) (13). There is reason to suppose that absorption of penicillin G would be similarly affected (14).
	Ticarcillin has been shown to reduce the antibacterial activity of gentamicin <i>in vivo</i> . If the two agents are clinically indicated, they should be given at different times (5).
	Gentamicin and carbenicillin are incompatible when mixed <i>in vitro</i> . Lower blood levels of gentamicin than expected are achieved by such admixture (30, 31).
<b>Oral contraceptives/ aminoglycoside antibiotics</b> (18)	Neomycin may impair the absorption of oral contraceptives, whose efficacy is therefore reduced giving rise to a risk of unwanted pregnancy.
<b>Vitamin K/aminoglycoside antibiotics</b> (10, 15-17)	Aminoglycoside antibiotics have been shown to decrease vitamin K production by the intestinal flora and thus increase the prothrombin time.

## 5.2. CEPHALOSPORINS AND RELATED $\beta$ -LACTAM ANTIBIOTICS

INN approved name:

<b>Atreonam</b>	<b>Ceftazidime</b>
<b>Cefaclor</b>	<b>Ceftizoxime</b>
<b>Cefadroxil</b>	<b>Ceftriaxone</b>
<b>Cefixime</b>	<b>Cefuroxime</b>
<b>Cefodizime</b>	<b>Cephalexin</b>
<b>Cefoperazone</b>	<b>Cephamandole</b>
<b>Cefotaxime</b>	<b>Cephazolin</b>
<b>Cefoxitin</b>	<b>Imipenem (with Cilastatin)</b>
<b>Cefpodoxime</b>	<b>Latamoxef</b>
<b>Cefsuladin</b>	

As a group, the cephalosporins do not create major problems due to interactions but individual members of the group have some specific interactions.

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/cephalosporin antibiotics</b> e.g. cephamandole cefoperazone latamoxef (1, 35–37)	‘Antabuse-like’ effects have been reported in patients taking concomitant cephalosporins and other $\beta$ -lactam antibiotics. The antibiotics incriminated are cephamandole, cefoperazone and latamoxef.
<b>Anticoagulants/cephalosporin antibiotics</b> e.g. cephamandole latamoxef (1, 35, 39)	Anticoagulant effect of warfarin and nicoumalone enhanced by cephamandole and others, including latamoxef. Latamoxef has been associated with serious bleeding and hypoprothrombinaemia even in patients who have not been anticoagulated. The risk of serious adverse reaction in anticoagulated patients cannot be underestimated.
<b>Colistin/cephalosporin antibiotics</b> (38)	The combination of cephalosporin antibiotics with colistin (a polymyxin antibiotic) is alleged to increase risk of renal damage.

<i>Combination</i>	<i>Interaction</i>
<b>H<sub>2</sub> antagonists/ cephalosporin antibiotics</b> (1)	H <sub>2</sub> antagonists reduce the absorption of cefpodoxime.
<b>Probenecid/cephalosporin antibiotics</b> (1, 39, 40)	Probenecid increases the plasma levels of most cephalosporin antibiotics due to reduced renal clearance.

### 5.3. CHLORAMPHENICOL AND THIAMPHENICOL

INN approved name:

**Chloramphenicol**

**Thiamphenicol**

The drug interactions referred to below refer to systemic use of chloramphenicol and not to use of ophthalmic preparations.

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulants/ chloramphenicol</b> e.g. warfarin nicoumalone phenindione (16, 41)	Chloramphenicol decreases the vitamin K production by intestinal bacteria and also directly inhibits the metabolism of coumarin anticoagulants in the liver. Both mechanisms of action enhance the anticoagulant effect of coumarins.
<b>Antidiabetic agents/ chloramphenicol</b> e.g. sulphonylurea hypoglycaemic agents (41, 42)	Chloramphenicol 2 g/day for 10 days has been shown to result in a three-fold increase in the half-life of tolbutamide and other sulphonylurea derivatives. Profound hypoglycaemia can ensue (41). Similarly, chloramphenicol increased the half-life of chlorpropamide from 30–36 to a range of 40–146 hr (42).
<b>Antiepileptic agents/ chloramphenicol</b> e.g. phenobarbitone phenytoin (41, 43, 44)	Chloramphenicol's metabolism is accelerated by the enzyme-inducing effects of phenobarbitone leading to reduced chloramphenicol plasma levels. Conversely, chloramphenicol inhibits the hepatic metabolism of phenytoin which may be given to epileptics with phenobarbitone. Phenytoin plasma levels can rise to such an extent that toxicity occurs. (A study in two

<i>Combination</i>	<i>Interaction</i>
<b>Antiepileptic agents/ chloramphenicol cont.</b>	patients showed phenytoin half-life to increase from 9.0 and 10.5 hr to 12. 5 and 22.0 hr, respectively (41).)
	Phenytoin can also lead to increases in the blood levels of chloramphenicol due to competition for hepatic metabolic binding sites. This has been associated with blood dyscrasias.
<b>Cimetidine/ chloramphenicol (45, 46)</b>	Fatal aplastic anaemia of unusually precipitate onset has been reported in two patients who received intravenous chloramphenical and cimetidine simultaneously.
<b>Cyclophosphamide/ chloramphenicol (47)</b>	Administration of chloramphenicol prior to cyclophosphamide prolonged the mean cyclophosphamide half-life from 7.5 to 11.5 hr.
<b>Oral contraceptives/ chloramphenicol (48)</b>	Isolated cases of unwanted pregnancy have been reported in women on oral contraception who have received chloramphenicol.
<b>Paracetamol/ chloramphenicol (49–56)</b>	Contradictory reports of the presence or absence of an interaction between paracetamol and chloramphenicol have appeared in the literature. Prescott (1996) reviewed the literature of seven papers, three showed no effect, one showed greatly increased paracetamol half-life from 3.25 to 15.0 hr (50). This was attributed to competition for glucuronide conjugation. Three (53–55) showed an increased rate of paracetamol metabolism.
<b>Penicillin antibiotics/ chloramphenicol</b>	Bacteriostatic and bactericidal antibiotics should not be combined. A bacteriostatic agent such as chloramphenicol can inhibit the bactericidal actions of penicillins.

### 5.4. CLINDAMYCIN

INN approved name:  
**Clindamycin**

The propensity of clindamycin to produce pseudomembranous colitis limits clinical usefulness.

<i>Combination</i>	<i>Interaction</i>
<b>Cholinergics/clindamycin</b> e.g. neostigmine pyridostigmine (1)	Antagonizes the effect of neostigmine used in myasthenia gravis and pyridostigmine used in glaucoma.
<b>Muscle relaxants/ clindamycin</b> (1, 63, 64)	Potentiates the effect of non-depolarizing muscle relaxants such as tubocurarine and fazidinium bromide.

### 5.5. FUSIDIC ACID

INN approved name:  
**Sodium fusidate**

Sodium fusidate is excreted mainly in the bile, little or none being excreted in the urine. The manufacturer recommends that caution is used if sodium fusidate is administered with other antibiotics which have a similar biliary excretion pathway, e.g. lincomycin and rifampicin. Although fusidic acid has been shown to displace bilirubin from plasma binding which could be relevant with respect to displacement of other drugs from plasma binding, no interactions of clinical relevance have been reported.

### 5.6. GLYCOPEPTIDE ANTIBIOTICS

INN approved name:  
**Vancomycin**  
**Teicoplanin**

Both vancomycin and teicoplanin have been reported to show ototoxicity and vancomycin can cause nephrotoxicity and renal failure.

<i>Combination</i>	<i>Interaction</i>
<b>Anaesthetic agents/ glycopeptide antibiotics</b> (65)	Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema, histamine-like flushing and anaphylactoid reactions.

<i>Combination</i>	<i>Interaction</i>
<b>Aminoglycosides/ glycopeptide (66)</b>	Teicoplanin is claimed not to have synergistic ototoxic or nephrotoxic effects with aminoglycoside antibiotics. Consequently teicoplanin with gentamicin is recommended as an alternative to vancomycin and gentamicin for endocarditis prophylaxis.

## 5.7. IMIDAZOLES

### Imidazole antibacterials

INN approved name:

**Metronidazole**

**Tinidazole**

### Imidazole antifungals

INN approved name:

**\*Clotrimazole**

**\*Econazole**

**Fluconazole**

**Isoconazole**

**Itraconazole**

**Ketoconazole**

**Miconazole**

**\*Sulconazole**

**\*Triconazole**

\*Not used systemically, only as skin or vaginal formulations.

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/imidazoles (67, 68)</b>	Metronidazole has pronounced Antabuse effect. Alcohol should not be taken during or for 48 hr after metronidazole therapy. Ketoconazole also interacts with alcohol.
<b>Antacids/imidazoles</b>	Antacids reduce absorption of imidazoles.
<b>Anticoagulants/imidazoles (67)</b>	Enhanced anticoagulant effect of nicoumalone and warfarin due to inhibition of metabolism by metronidazole. This is due to the stereoselective inhibition of the metabolism of the S-isomer of warfarin (124, 125).
<b>Anti-epileptic/ imidazoles (67)</b>	Metronidazole inhibits metabolism of phenytoin and increases plasma levels. Phenobarbitone accelerates metabolism of metronidazole. Ketoconazole

<i>Combination</i>	<i>Interaction</i>
<b>Cisapride/imidazoles</b> (246)	metabolism accelerated by phenytoin and phenobarbitone.
<b>Cytotoxics/imidazoles</b> (70–78)	Cisapride should not be co-administered with oral or parenteral fluconazole, itraconazole, ketoconazole or miconazole because of risk of ventricular arrhythmias and <i>torsade des pointes</i> .
<b>Disulfiram/imidazoles</b> (80)	Ketoconazole inhibits metabolism (70–79) of cyclosporin. Metronidazole inhibits the metabolism of fluorouracil (79).
<b>Lithium/imidazoles</b> (67, 69)	Psychotic reactions reported. Imidazoles and disulfiram inhibit hepatic metabolism.
<b>H<sub>1</sub> Antagonists/ imidazoles</b> (81, 82, 92, 93)	Increased lithium toxicity has been reported. Two women experienced toxic reactions to long-term lithium treatment following the brief use of metronidazole to treat vaginitis. In both cases marked increases in urine output were observed and diagnoses of nephrogenic diabetes insipidus was made.
<b>H<sub>2</sub> Antagonists/ imidazoles</b> (1, 83)	Metabolism of astemizole and terfenadine inhibited with increased risk of ventricular arrhythmias, including <i>torsade des pointes</i> .
<b>Midazolam/imidazoles</b> (84)	H <sub>2</sub> antagonists, also the protein pump inhibitor omeprazole, and sucralfate, reduce absorption of ketoconazole and itraconazole. Cimetidine inhibits the metabolism of metronidazole and gives increased metronidazole blood levels with increased CNS side effects.
<b>Rifampicin/imidazoles</b> (85–87)	Itraconazole was shown to inhibit (84) the hepatic clearance of midazolam due to impaired hydroxylation. The area under the curve increased sixfold in a study of 12 volunteers.
	Rifampicin given by mouth or intravenously has reduced the plasma concentrations of ketoconazole and led to failure of antifungal treatment. If isoniazid was also given a further fall in ketoconazole levels occurred (86).

## 5.8. MACROLIDE ANTIBIOTICS

INN approved name:

**Azithromycin**

**Midecamycin**

**Clarithromycin**

**Oleandomycin**

**Erythromycin**

**Spiramycin**

**Josamycin**

**Triacetyloleandomycin**

The most significant interactions of macrolide antibiotics with other therapeutic substances is due to their ability to inhibit the hepatic metabolism of other substances. The effects on inhibition of cytochrome P450 are most marked after triacetyloleandomycin, marked after erythromycin and clarithromycin and least after josamycin, midecamycin or spiramycin (88).

<i>Combination</i>	<i>Interaction</i>
<b>Analgesics/macrolide antibiotic (89)</b>	Plasma concentration of alfentanil (89) increased by erythromycin.
<b>Antacids/macrolide antibiotic (89)</b>	Reduce absorption of azithromycin (89) from gut.
<b>Antiarrhythmics/macrolide antibiotic e.g. disopyramide (90)</b>	Plasma concentration of disopyramide increased by erythromycin. Ventricular tachycardia and other ventricular dysrrhythmias have been reported.
<b>Anticoagulants/macrolide antibiotic e.g. warfarin nicoumalone (91)</b>	Anticoagulant effect of nicoumalone and warfarin enhanced by macrolide antibiotics due to inhibition of metabolism.
<b>Antihistamines/macrolide antibiotic e.g. astemizole terfenadine (81, 82, 92, 93)</b>	Macrolide antibiotics inhibit the metabolism of the non-sedating antihistamines, astemizole and terfenadine. This interaction can lead to overdosage with these antihistamines and cardiotoxicity in the form of ventricular arrhythmias including <i>torsade des pointes</i> . (Similar interactions have been reported with ketoconazole and itraconazole with terfenadine.)
<b>Antiepileptics/macrolide antibiotic e.g. carbamazepine phenytoin (94–98)</b>	Clarithromycin and erythromycin inhibit the metabolism of carbamazepine and phenytoin and enhance their potential for side effects.

<i>Combination</i>	<i>Interaction</i>
<b>Benzodiazepines/ macrolide antibiotic</b> e.g. midazolam (1)	Erythromycin inhibits the metabolism of midazolam and increases the plasma level significantly.
<b>Cardiac glycosides/ macrolide antibiotic</b> e.g. digoxin (99–102)	Erythromycin inhibits the metabolism of digoxin and can therefore precipitate digoxin toxicity. This is believed to be partly due to inhibition of hepatic metabolism, but gut flora also breakdown digoxin and this is inhibited by erythromycin and tetracyclines.
<b>Cisapride/macrolide antibiotic</b> (246)	The co-administration of cisapride and erythromycin or clarithromycin can lead to prolongation of QT interval, ventricular dyrrhythmia and <i>torsade des pointes</i> .
<b>Corticosteroids/macrolide antibiotic</b>	Due to inhibition of cytochrome P450 the breakdown of steroid hormones is inhibited.
<b>Cyclosporin/macrolide antibiotic</b> (103–107)	Erythromycin inhibits the hepatic metabolism of cyclosporin and increases risk of renal damage.
<b>Ergotamine/macrolide antibiotic</b> (108–109)	Erythromycin has been reported to inhibit the metabolism of ergotamine to the extent of producing clinical ergotism.
<b>Dopaminergics/macrolide antibiotic</b> e.g. bromocriptine (110)	Erythromycin has been shown to inhibit bromocriptine metabolism. Peak plasma levels were found to be increased by 400% in five healthy subjects.
<b>Xanthines/macrolide antibiotic</b> (111–113) e.g. theophylline	Triacetyloleandomycin, clarithromycin and erythromycin inhibit the hepatic metabolism of theophylline and increase the risk of toxicity. The kinetics of theophylline were unaltered by josamycin, midecamycin and spiramycin (114, 115).
<b>Zidovudine/macrolide antibiotic</b> (1)	Clarithromycin reduces the absorption (1) of zidovudine.

### 5.9. NITROFURANS

INN approved name:  
**Nitrofurantoin**

<i>Combination</i>	<i>Interaction</i>
<b>Antacids/nitrofurantoin</b> (1)	Antacids, e.g. magnesium trisilicate reduce nitrofurantoin absorption.
<b>Anticonvulsants/nitrofurantoin</b> e.g. phenytoin (116)	A fall in serum phenytoin levels and resultant loss of seizure control has been reported in a patient in whom nitrofurantoin was added to therapy.
<b>Oral contraceptives/nitrofurantoin</b> (117)	Nitrofurantoin like other antibiotics may reduce the efficacy of oral contraceptives.
<b>4-Quinolones/nitrofurantoin</b> e.g. nalidixic acid (118)	Nitrofurantoin inhibits the antibacterial action of nalidixic acid. The concomitant use of these two agents in urinary tract infections should be avoided.
<b>Uricosurics/nitrofurantoin</b> e.g. probenecid (1, 118)	Reduces renal clearance of nitrofurantoin and, therefore, increases its risk of toxicity.

### 5.10. PENICILLINS

INN approved name:  
**Benzyl penicillin**  
**Phenoxyethyl penicillin (Penicillin V)**  
**Procaine penicillin**

#### Penicillinase Resistant Penicillins

**Cloxacillin**  
**Flucloxacillin**  
**Temocillin**

#### Broad Spectrum Penicillins

<b>Amoxycillin</b>	<b>Amoxycillin + clavulanic acid (Co-fluampicil)</b>
<b>Ampicillin</b>	<b>Pivampicillin</b>
<b>Ampicillin + cloxacillin</b>	<b>Pivampicillin + pivmecillinam</b>
<b>Bacampicillin</b>	

**Antipseudomonal Penicillins**

**Azlocillin**  
**Carbenicillin**  
**Piperacillin**  
**Ticarcillin**

**Mecillinams**

**Pivmecillinam** (see combination with pivampicillin)

Very few interactions between penicillins and other medication are clinically significant.

<i>Combination</i>	<i>Interaction</i>
<b>Antacids/penicillin</b>	Antacids reduce absorption of pivampicillin
<b>Allopurinol/penicillin</b> (119–120)	A survey by the Boston Drug Collaborative Surveillance Program has shown that the administration of allopurinol to patients receiving ampicillin or amoxycillin doubled or quadrupled, respectively, the incidence of rashes.
<b>Anticoagulants/penicillin</b>	Broad spectrum penicillins can potentiate the effect of anticoagulants by reducing vitamin K synthesis by bowel flora.
<b>Antimalarial agents/penicillin</b>	Chloroquine reduces the bioavailability of ampicillin following oral co-administration (126)
<b>Cefotaxime/penicillin</b> (127–128)	There are reports of encephalopathy and focal seizures in patients with renal failure given cefotaxime with azlocillin (127, 128).
<b>Cytotoxics/penicillin</b> e.g. methotrexate	Penicillins reduce the excretion of methotrexate and therefore increases the risk of methotrexate toxicity.
<b>Gentamicin/penicillin</b> (121, 122)	Simultaneous treatment intravenously with carbenicillin and gentamicin has been shown to cause a profound fall in gentamicin blood levels. This appears to be an <i>in vitro</i> interaction.

<i>Combination</i>	<i>Interaction</i>
<b>Guar-gum/penicillin (124)</b>	Guar-gum reduces the absorption of phenoxyethyl penicillin.
<b>Muscle relaxants/penicillin (1)</b>	Azlocillin increases the effect of non-depolarizing muscle relaxants such as tubocurarine.
<b>Neomycin/penicillin (124)</b>	Oral neomycin has been shown to reduce the absorption of phenoxyethyl penicillin (Penicillin V)
<b>Probenecid/penicillin (129)</b>	Probenecid reduces the renal excretion of penicillin.
<b>Oral contraceptives/penicillin (117)</b>	Pregnancies have been reported in women taking oral contraceptives who were also given ampicillin. It is now thought only to occur in women who get antibiotic-associated diarrhoea and therefore malabsorption of oestrogen and progestogen components of the 'Pill'.

### 5.11. POLYMYXINS

INN approved name:  
**Colistin**

Colistin is not absorbed by mouth and is used in bowel sterilization regimes. It has to be given by injection to obtain a systemic effect. Interactions are largely as for aminoglycoside antibiotics (see Part 2, Chapter 1).

<i>Combination</i>	<i>Interaction</i>
<b>Cephalosporin/colistin (38)</b>	The combination of colistin with a cephalosporin antibiotic increases the risk of renal damage.
<b>Muscle relaxants/colistin (130–133)</b>	Colistin enhances neuromuscular blocking effect of non-depolarizing muscle relaxants, e.g. tubocurarine, fentanyl bromide, etc. This effect is enhanced by K <sup>+</sup> depletion or low ionized serum Ca <sup>2+</sup> . Cholinergic agents are of little value in reversing this prolongation of action.

## 5.12. 4-QUINOLONES

### Products

INN approved name:

<b>Acrosoxacin</b>	<b>Nalidixic acid</b>
<b>Ciprofloxacin</b>	<b>Norfloxacin</b>
<b>Cinoxacin</b>	<b>Pefloxacin</b>
<b>Enoxacin</b>	<b>Ofloxacin</b>

This class of antibacterials enter into interactions because they chelate with cations such as calcium, magnesium, iron, aluminium and zinc, which reduces their absorption. 4-quinolones inhibit hepatic metabolism.

<i>Combination</i>	<i>Interaction</i>
<b>Combination</b> <b>Analgesics/NSAIDs/ quinolone antibiotic (134–136)</b>	<b>Interaction</b> Both the Japanese and UK regulatory authorities have issued warnings of an increased risk of convulsions when 4-quinolones and NSAIDs are administered. The mechanism of this interaction is not known.
<b>Antacids containing aluminium, bismuth, calcium, magnesium cations /quinolone antibiotic (137, 138)</b>	Cations bind with 4-quinolones to produce a non-absorbable complex.
<b>Anti-ulcer agent sucralfate/quinolone antibiotic e.g. cimetidine (139, 140) ranitidine (141)</b>	Sucralfate releases aluminium cations in the stomach which causes impaired absorption of 4-quinolones. Cimetidine has been reported to reduce the clearance of pefloxacin. Intravenous ranitidine has been reported to reduce the bioavailability of oral enoxacin.
<b>Anticoagulants/quinolone antibiotic e.g. warfarin nicoumalone (142–148)</b>	The effect of coumarin anticoagulants is enhanced due to certain 4-quinolones, namely, ciprofloxacin (142, 143), nalidixic acid (144–146), ofloxacin (147), enoxacin (148), slowing the hepatic metabolism of warfarin and nicoumalone.

<i>Combination</i>	<i>Interaction</i>
<b>Antidiabetic agents/ quinolone antibiotic sulphonylurea</b> (127, 128)	The hepatic metabolism of sulphonylurea antidiabetic agents is impaired by 4-quinolones. Hypoglycaemic effect is therefore enhanced.
<b>Iron and zinc salts also</b> <b>Milk and dairy products/quinolone antibiotic</b> (149–151)	Cations bind with 4-quinolones also and reduce their absorption. This effect involves iron given for anaemia and all dairy products, all of which contain $\text{Ca}^{2+}$ cations.
<b>Nitrofurantoin/quinolone antibiotics</b> (152, 153)	Nitrofurantoin inhibits the antibacterial action of nalidixic acid and other 4-quinolones. The concomitant use of the two drugs to treat urinary tract infections is contraindicated.
<b>Penicillins/quinolone antibiotics</b> (154)	The simultaneous administration of parenteral ciprofloxacin with azlocillin has resulted in higher and more prolonged serum concentrations of ciprofloxacin.
<b>Probenecid/quinolone antibiotics</b> (1)	The renal excretion of cinoxacin is reduced by probenecid. A similar effect has been described with nalidixic acid and ciprofloxacin.
<b>Xanthines/quinolone antibiotics</b> (155–161)	To a greater or lesser extent, all 4-quinolones reduce the hepatic clearance of xanthines such as theophylline and caffeine and increase the risk of toxicity. Seizures have occurred in patients given ciprofloxacin and theophylline simultaneously.

### 5.13. SULPHONAMIDES

The use of sulphonamides has decreased in recent years as a result of increasing bacterial resistance and their replacement by more effective and less toxic alternatives. the large range of sulphonamides once used clinically is now reduced to three or four.

The principle side effects of this group of drugs is nausea, vomiting, anorexia and diarrhoea. The more serious adverse reactions include toxic epidermal necrosis, Stevens-Johnson syndrome, lupus erythematosus, nephrotoxic reactions. Severe myelosuppression including aplastic anaemia and agranulocytosis are unfortunately not as rare as some would have us believe. There is little justification for the

continued use of co-trimoxazole since it has no advantages over trimethoprim alone (see Cribb *et al.*, 1996).

**INN approved name:**

**Co-trimoxazole** (combination of trimethoprim and sulphamethoxazole)

**Sulphadiazine**

**Sulphadimidine**

**Sulfametopyrazine**

Interactions of sulphonamides with other therapeutic agents hinges on their antifolate actions, on their ability to displace other drugs from plasma binding sites, and on inhibition of a number of metabolic processes.

<i>Combination</i>	<i>Interaction</i>
<b>Anaesthetics/ sulphonamide</b> e.g. thiopentone (162)	Sulphonamides increase effect of thiopentone due to reduced plasma binding of thiopentone.
<b>Anticoagulants/ sulphonamide</b> e.g. nicoumalone warfarin (38, 163)	Sulphonamides reduce amount of vitamin K synthesized by intestinal flora. They also displace coumarin anticoagulants from plasma protein binding sites and, by both actions, potentiate their anticoagulant effect.
<b>Antidiabetic agents/ sulphonamide</b> e.g. sulphonylureas (12, 164–166)	Sulphonamides inhibit the carboxylation of tolbutamide. They also displace tolbutamide from plasma protein binding sites. Sulphonamides also displace chlorpropamide from plasma binding sites. Hypoglycaemic action enhanced.
<b>Antiepileptic agents/ sulphonamide</b> e.g. phenytoin (1, 167–169)	Antifolate effect of phenytoin increased. Plasma concentration of phenytoin increased. Increased risk of phenytoin toxicity.
<b>Cyclosporin/ sulphonamide</b> (170, 171)	Increased risk of nephrotoxicity when given in combination. Cyclosporin falls to non-therapeutic levels, increased risk of rejection of organ transplant.

<i>Combination</i>	<i>Interaction</i>
<b>Cytotoxics/sulphonamide</b> e.g. methotrexate (12, 172)	Sulphonamides displace methotrexate from plasma protein binding sites and thus increase its toxicity. Sulphonamides also increase antifolate action of methotrexate.
<b>Local anaesthetics/ sulphonamide</b> e.g. amethocaine benzocaine butacaine procaine (173, 174)	Local anaesthetics which are derivatives of <i>p</i> -aminobenzoic acid are hydrolyzed in the body to <i>p</i> -aminobenzoic acid and should not be used in patients being treated with sulphonamides. Sulphonamides exert their antibacterial action by competitive inhibition of <i>p</i> -aminobenzoic acid in the micro-organism.

## 5.14. TETRACYCLINES

INN approved name:

**Tetracycline** also compound formulations with Nystatin

**Demeclocycline**

**Doxycycline**

**Lymecycline**

**Minocycline**

**Oxytetracycline**

The absorption of tetracyclines is reduced by divalent and trivalent cations, e.g. aluminium, bismuth, calcium, iron, magnesium and zinc. Such interactions by which tetracyclines form non-absorbable complexes with these cations will also affect certain excipients used in other pharmaceuticals and the calcium in all milk and dairy products. Dental discolouration is a major disadvantage to their use in pregnancy and children principally affecting non-erupted teeth.

<i>Combination</i>	<i>Interaction</i>
<b>Antiulcer drugs/ tetracyclines</b> e.g. sucralfate $\text{Al}^{2+}$ - and $\text{Ca}^{2+}$ - containing antacids (175–177, 180)	Sucralfate releases aluminium cations in the stomach which leads to impaired tetracycline absorption.

<i>Combination</i>	<i>Interaction</i>
<b>Cimetidine/tetracyclines</b> (181–183)	Co-administration of cimetidine 1000 mg daily for 3 days reduced the absorption of tetracycline.
<b>Anticoagulants/tetracyclines</b> (16, 178)	Tetracyclines have been shown to reduce plasma prothrombin activity by impairing prothrombin utilization. Tetracyclines also decrease vitamin K production by intestinal bacteria. Both these mechanisms tend to result in potentiation of anticoagulant activity.
<b>Anticonvulsants/tetracyclines</b> e.g. carbamazepine phenobarbitone phenytoin (179, 180)	The plasma half-life of doxycycline in 25 control subjects was 15.1 hr. In epileptic patients treated with enzyme-inducing anti-epileptic agents the plasma half-life of doxycycline was of the order of 7.2–7.4 hr.
<b>Oral hypoglycaemic agents/tetracyclines</b> e.g. phenformin (184, 183, 186)	Tetracyclines given to patients whose diabetes is controlled on phenformin can produce lactic acidosis.
<b>Iron salts/tetracyclines</b> (177)	Fe <sup>2+</sup> ions impair tetracycline absorption due to formation of insoluble complexes.
<b>Milk and milk products/tetracyclines</b> e.g. cheese and butter (177)	Ca <sup>2+</sup> ions in milk and milk products impair tetracycline absorption due to the formation of insoluble complexes.
<b>Digoxin/tetracyclines</b> (187, 188)	Tetracyclines may produce raised plasma levels of digoxin.
<b>Lithium/tetracyclines</b> (189)	Tetracyclines may produce raised lithium levels
<b>Penicillins/tetracyclines</b> (190)	Bactericidal and bacteriostatic antimicrobials should not be co-administered, since the efficacy of the bactericidal component is reduced.

<i>Combination</i>	<i>Interaction</i>
<b>Retinoids/tetracyclines (191–192)</b>	<p>Retinoids, like tetracycline, are used in the treatment of acne. There is an increased incidence of benign intracranial hypertension when these agents are co-administered. The mechanism of drug-induced benign intracranial hypertension is unknown.</p> <p>A review of the WHO Collaborative Centre data base and Spontaneous ADR reports to the Committee on Safety of Medicines and of the world literature indicated that both tetracyclines alone, retinoids alone, and the two drugs in combination were one of the commonest causes of pseudotumour cerebri (191).</p>

## 5.15. TRIMETHOPRIM

INN approved name:

**Trimethoprim** (see also Co-trimoxazole)

<i>Combination</i>	<i>Interaction</i>
<b>Anti-arrhythmics/ trimethoprim (procainamide) (193)</b>	Plasma concentrations of procainamide increased. A peculiar aseptic meningitis has been reported in association with trimethoprim therapy.
<b>Anticoagulants/ trimethoprim (nicoumalone and warfarin) (189)</b>	Effects of nicoumalone and warfarin are enhanced.
<b>Antidiabetics/ trimethoprim (sulphonylureas) (193)</b>	Hypoglycaemic effect of sulphonylureas is increased.
<b>Anti-epileptics/ trimethoprim (phenytoin) (189)</b>	Trimethoprin increases the elimination half-life of phenytoin (194).

<i>Combination</i>	<i>Interaction</i>
<b>Antimalarials/ trimethoprim (pyrimethamine) (193)</b>	The antifolate effects of phenytoin, pyrimethamine and methotrexate are all enhanced by trimethoprim.
<b>Cytotoxics/trimethoprim (methotrexate) (193)</b>	
<b>Digoxin/trimethoprim (194)</b>	Trimethoprim increases the elimination half-life of digoxin.
<b>Rifampicin/trimethoprim (193, 194)</b>	Rifampicin reduces trimethoprim blood levels.

## 5.16. ANTITUBERCULOUS AGENTS

INN approved name:

### 1. Streptomycin

For interactions see aminoglycoside antibiotics.

### 2. Rifampicin

### 3. Rifabutin

Most interactions relate to increased metabolic breakdown induced by rifampicin.

<i>Combination</i>	<i>Interaction</i>
<b>Analgesics/rifampicin (1, 199, 209)</b>	Rifampicin increases the metabolism of methadone and reduces its analgesic effect.
<b>Anticoagulants/rifampicin (coumarins) (1, 199)</b>	Metabolism of nicoumalone and warfarin accelerated, therefore reduced effect.
<b>Antidepressants/ rifampicin (tricyclics) (1, 199)</b>	Metabolism of most tricyclic antidepressants accelerated, therefore reduced effect.
<b>Antidiabetic agents/ rifampicin (1, 199)</b>	Metabolism of sulphonylurea oral hypoglycaemics increased with reduction in their efficacy.

<i>Combination</i>	<i>Interaction</i>
<b>Anti-epileptics/ rifampicin</b> e.g. phenytoin phenobarbitone (1, 199)	Reduced plasma concentration of phenytoin and loss of control of epilepsy due to increased rate of metabolism.
<b>Antibacterials and antifungals/rifampicin</b> (imidazoles) (199)	Metabolism increased and effectiveness of imidazoles reduced.
<b>Antipsychotics/rifampicin</b> (haloperidol) (199)	Rate of metabolism of haloperidol increased and efficacy therefore reduced.
<b>Benzodiazepines/ rifampicin</b> (199)	Rate of metabolism increased.
<b>β-adrenergic blockers/ rifampicin</b> (199, 208)	Metabolism of β-blockers increased.
<b>Calcium channel blockers/rifampicin</b> (1, 199)	Metabolism of diltiazam, verapamil and nifedipine accelerated.
<b>Cardiac glycosides/ rifampicin</b> (1, 199, 205–207)	Metabolism of digoxin (199, 205) and digitoxin (206, 207) increased with reduced efficacy.
<b>Corticosteroids, oestrogens and progestogens/rifampicin</b> (199–204)	All steroid hormone metabolism and increased. Reduced efficacy of <i>all</i> oral contraceptives with increased risk of failure.
<b>Cyclosporin/rifampicin</b> (198)	Increased rate of metabolism of cyclosporin and reduced immunosuppression and increased risk of transplant rejection.
<b>H<sub>2</sub>-blockers/rifampicin</b> (cimetidine) (199)	Increased rate of metabolism.

<i>Combination</i>	<i>Interaction</i>
<b>Quinine/rifampicin</b> (195, 196)	Rifampicin reduced the blood levels of quinine and increased the rate of elimination six-fold.
<b>Theophylline/rifampicin</b> (197)	Reduced plasma theophylline level due to increased metabolism.
<b>Thyroxine/rifampicin</b> (199)	Increased rate of metabolism may cause increased requirements to treat hypothyroid patients.

#### 4. Capreomycin

The adverse effects of capreomycin on the eighth nerve and kidney are similar to the aminoglycoside antibiotics. Capreomycin also has a neuromuscular blocking effect and may therefore interact with skeletal muscle relaxants.

<i>Combination</i>	<i>Interaction</i>
<b>Antibiotics/capreomycin</b> (216)	Increased rate of nephrotoxicity with concomitant use of capreomycin and colistin.
<b>Aminoglycosides and glycopeptide antibiotics/capreomycin</b> (216)	Increased rate of nephrotoxicity and ototoxicity when used in combination with an aminoglycoside antibiotic or vancomycin.
<b>Cytotoxics/capreomycin</b> (cisplatin) (216)	Capreomycin used in combination with cisplatin carries an increased risk of both nephrotoxicity and ototoxicity.
<b>Streptomycin/capreomycin</b> (216)	This combination carries an increased risk of ototoxicity above that of either drug given alone.

#### 5. Isoniazid

There is increased risk of isoniazid toxicity in patients who are slow acetylators. This pharmacogenetic dysmorphism is also relevant in manifestation of interactions. Most interactions are due to isoniazid-induced metabolic inhibition which is greater in slow acetylators.

Isoniazid does have monoamine oxidase-inhibiting properties and can thus interact with foods that have a high tyramine content, e.g. Swiss cheese (210), red wines particularly Chianti (211), tuna fish and other fish with a high histamine content (212–215).

<i>Combination</i>	<i>Interaction</i>
<b>Antacids and Absorbants/ isoniazid</b>	Reduced absorption of isoniazid.
<b>Antibiotics/isoniazid (cycloserine) (222)</b>	Increased CNS toxicity of cycloserine due to isoniazid inhibition of its metabolism.
<b>Anti-epileptics/isoniazid e.g. carbamazepine ethosuximide phenytoin (1, 217–220)</b>	Isoniazid inhibits the hepatic metabolism of these anti-epileptics and increases risk of toxicity.
<b>Benzodiazepines/isoniazid e.g. diazepam</b>	Metabolism of diazepam is inhibited.
<b>Xanthines/isoniazid (theophylline) (221)</b>	Isoniazid increases plasma levels of theophylline.

## 6. Cycloserine

Cycloserine is contraindicated in patients with epilepsy, depression, renal insufficiency or alcohol abuse.

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/cycloserine (223)</b>	Cycloserine enhances the CNS effects of alcohol and concurrent use may induce convulsions.
<b>Antibiotics/cycloserine (isoniazid) (222)</b>	Isoniazid increases cycloserine plasma levels due to inhibition of hepatic metabolism. Therefore, increases CNS toxicity.
<b>Anti-epileptics/ cycloserine (phenytoin) (1)</b>	Cycloserine given to epileptics receiving phenytoin increases plasma concentration of phenytoin with increased risk of toxicity.

## 7. Other Antituberculous Agents

### *Ethambutol*

The most important adverse effect of ethambutol is retrobulbar neuritis with a reduction in visual activity, constriction of the visual field and central scotomata. Red-green colour blindness also occurs. Neutropenia may also occur, as may nephrotoxicity. Cholestatic jaundice has also been reported.

### *Pyrazinamide*

Hepatotoxicity is the most serious adverse reaction with pyrazinamide and, when given with isoniazid and rifampicin, the incidence is reported to be about 3%. Other side effects include arthralgia, fever, photosensitivity and rashes.

<i>Combination</i>	<i>Interaction</i>
<b>Antacids/ethambutol</b> (224)	Aluminium cations reduce the absorption of ethambutol.
<b>Uricosurics/pyrazinamide</b> (probenecid) (1, 225–227)	Probenecid reduces renal clearance of pyrazinamide (1, 227). Pyrazinamide itself reduces the elimination of urates by the kidney. Uricosuric therapy may be desirable in patients at risk of gout (225, 226).

## 5.17. ANTIFUNGAL AGENTS

INN approved name:

**Amphotericin**

**Flucytosine**

**Griseofulvin**

**Nystatin**

**Terbinafine**

**Triazole Compounds**

**Fluconazole**

**Itraconazole**

**Imidazole Antifungal Agents**

See section on imidazoles

## 1. Amphotericin

<i>Combination</i>	<i>Interaction</i>
<b>Antimicrobials/ amphotericin</b>	Potentiation of <i>in vitro</i> antiviral activity of acyclovir has been reported.
<b>Acyclovir/amphotericin (229)</b>	
<b>Flucytosine/ amphotericin (230)</b>	Mutual potentiation of antifungal action.
<b>Imidazole/amphotericin (233)</b>	Miconazole and amphotericin are antagonistic in their antifungal activity.
<b>Norfloxacin/amphotericin</b>	Antifungal activity may be enhanced by this combination.
<b>Rifampicin/amphotericin and</b> <b>Tetracycline/ amphotericin (231, 232)</b>	These combination of rifampicin and/or minocycline with amphotericin have been reported to have potentiated action against <i>Aspergillus</i> species.
<b>Cardiac glycosides/ amphotericin (173)</b>	Severe hypokalaemia may follow amphotericin therapy, this potentiates digitalis glycoside toxicity.
<b>Skeletal muscle relaxants/ amphotericin (173)</b>	The hypokalaemia associated with amphotericin may enhance the curariform action of skeletal muscle relaxants.

## 2. Flucytosine

<i>Combination</i>	<i>Interaction</i>
<b>Anticoagulants</b> <b>Nicoumalone and warfarin/flucytosine</b>	Flucytosine increases anticoagulant effects of nicoumalone and warfarin.
<b>Antidiabetic agents/ flucytosine (sulphonylureas)</b>	Sulphonylurea's hypoglycaemia effect potentiated.

<i>Combination</i>	<i>Interaction</i>
<b>Anti-epileptics/ flucytosine (173)</b>	Phenytoin metabolism inhibited, increased risk of toxicity.
<b>Cyclosporin/flucytosine</b>	Metabolism of cyclosporin inhibited; increased risk of nephrotoxicity.
<b>Rifampicin/flucytosine</b>	Rifampicin increases the rate of metabolism of flucytosine and reduces its efficacy.
<b>Theophylline/flucytosine</b>	Metabolism of theophylline inhibited. Increased risk of toxicity.

### 3. Griseofulvin

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/griseofulvin</b>	Griseofulvin may impair alcohol metabolism. Avoid alcohol.
<b>Anticonvulsants/ griseofulvin (11, 234, 235)</b>	Barbiturates and phenytoin increase the rate of inactivation of griseofulvin by liver microsomal P450 and reduces its antifungal efficacy.  Phenobarbitone has also been shown to impair the oral absorption of griseofulvin.
<b>Anticoagulants/ griseofulvin e.g. warfarin nicoumalone (15, 16, 236)</b>	Griseofulvin increases the rate of metabolism of coumarin-type anticoagulants.
<b>Bromocriptine/ griseofulvin (237)</b>	The response to bromocriptine was blocked in one reported case who was concurrently receiving griseofulvin.
<b>Cyclosporin/griseofulvin (238)</b>	The hepatic metabolism of cyclosporin is increased by griseofulvin leading to reduced efficacy of cyclosporin and risk of organ rejection in transplant patients.

<i>Combination</i>	<i>Interaction</i>
<b>Food/griseofulvin (239)</b>	Griseofulvin absorption is enhanced by fatty foods.
<b>Oral contraceptives/griseofulvin (240)</b>	The hepatic breakdown of oral contraceptives is increased by griseofulvin, thus increasing the risk of unwanted pregnancy.

#### 4. Nystatin

<i>Combination</i>	<i>Interaction</i>
<b>Riboflavin/nystatin</b>	The activity of nystatin against <i>Candida albicans</i> was completely inhibited by riboflavin.

### 5.18. ANTIVIRAL AGENTS

INN approved name:

<b>Acyclovir</b>	<b>Inosine pranobex</b>
<b>Amantadine hydrochloride</b>	<b>Pantamidine</b>
<b>Famciclovir</b>	<b>Tribavirin</b>
<b>Foscarnet sodium</b>	<b>Zidovudine</b>
<b>Ganciclovir</b>	

#### 1. Foscarnet

Foscarnet can produce renal damage, in some cases so serious that the patients have required dialysis.

<i>Combination</i>	<i>Interaction</i>
<b>Aminoglycosides/foscarnet (amphotericin B) (141)</b>	Renal toxicity of aminoglycosides and amphotericin are enhanced by foscarnet.
<b>Pentamidine/foscarnet (141)</b>	Renal impairment and symptomatic hypocalcaemia (Trousseau and Chvostek's signs) have been observed during concomitant foscarnet and i.v. pentamidine.

#### 2. Ganciclovir

The most common side effects of ganciclovir are haematological and include neutropenia, thrombocytopenia. Some degree of neutropenia occurs in 40% of patients treated. The manufacturer recommends that ganciclovir is not used with the following drugs; dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin,

amphotericin, trimethoprim, cotrimoxazole, because of the risk of addictive toxicity (242).

<i>Combination</i>	<i>Interaction</i>
<b><math>\beta</math>-lactam antibiotics/ganciclovir</b> e.g. imipen cilastatin (242)	Ganciclovir when used with combination of imipen and cilastatin has been reported to result in generalized seizures.
<b>Probenecid/ganciclovir</b> (242)	Probenecid increases the mean half-life and area under the plasma concentration of systemically administered acyclovir. Probenecid reduces the renal elimination of ganciclovir.

### 3. Zidovudine

Zidovudine should be used with caution with any agent which is potentially nephrotoxic, e.g. pentamidine, dapsone, amphotericin, fluocytosine, ganciclovir, interferon, vincristine, vinblastine, doxorubicin, etc. Experience of drug interaction potential is limited but the manufacturer warns that phenytoin blood levels should be monitored since reports are contradictory (244).

<i>Combination</i>	<i>Interaction</i>
<b>Ganciclovir/zidovudine</b> (243)	Unacceptable bone marrow toxicity occurred when zidovudine was added to ganciclovir in six of seven patients with AIDS – who had cytomegalovirus retinitis.

### Recommended further reading

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# **CHAPTER 6**

**Drug Interactions with Agents Used  
to Treat Endocrine Disorders**

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## 6.1 DRUGS USED IN DIABETES

### CLASSIFICATION OF ORAL ANTIDIABETIC AGENTS

Aldose reductase inhibitors	$\alpha$ -Glucosidase inhibitors	Biguanides	Sulphonylureas	Others
Alrestatin	Acarbose	Buformin	Acetohexamide	Gliquidone
Epalrestat	Emiglitate	Metformin	Carbutamide	Glisetide
Ponalrestat	Miglitol	Phenformin	Chlorpropamide	Glisolamide
			Glibenclamide	Glybuazole
			Glibornuride	Glymidine
			Glicloxepride	Guar Gum
			Gliclazide	Glycylamide
			Glimepiride	Tolazamide
			Glipizide	Tolbutamide

Source: Reynolds (1).

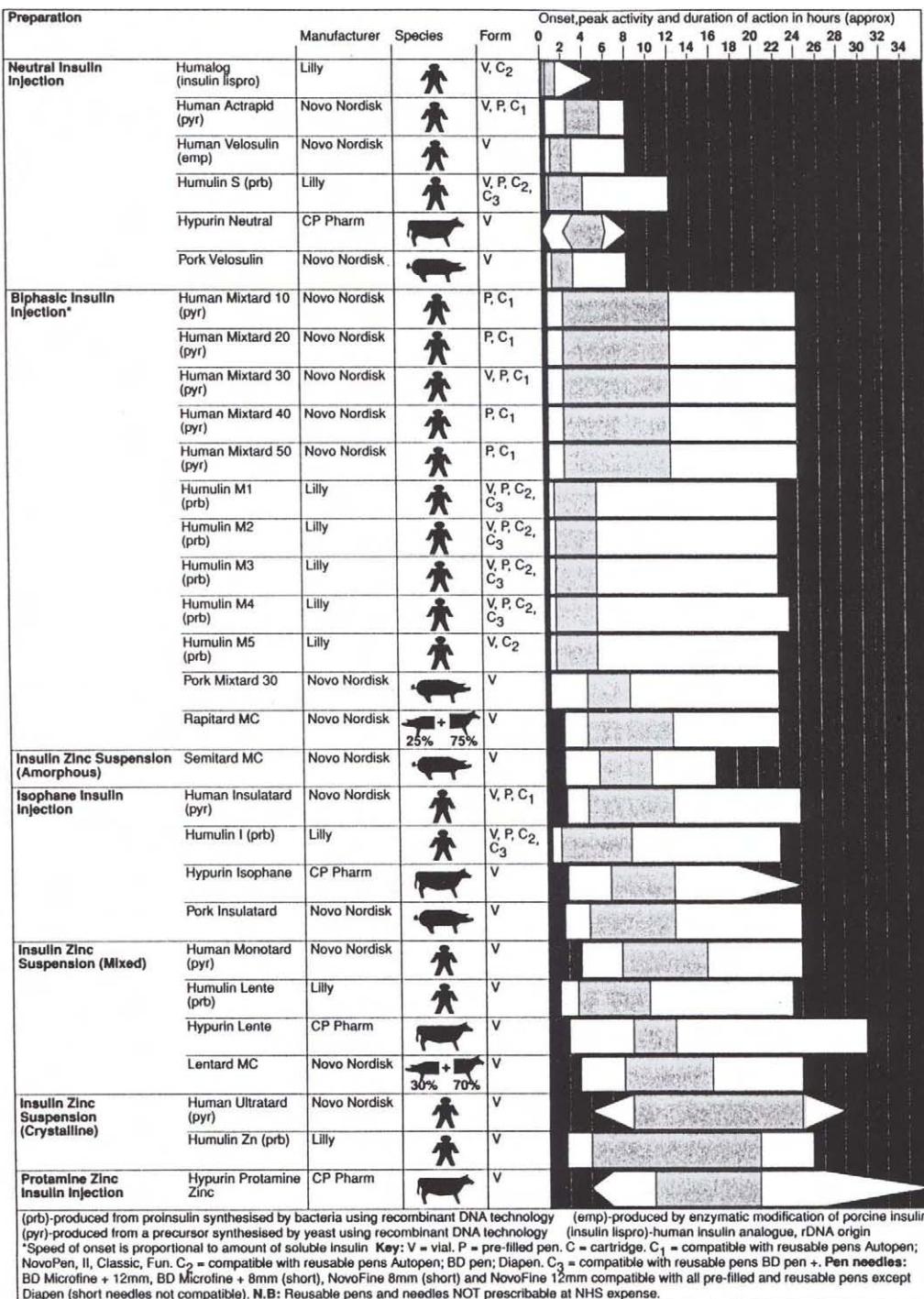
### CLASSIFICATION OF INSULINS

Insulin preparations marketed by British insulin manufacturers under *British Pharmacopoeia* titles are listed in the following table which is reproduced with the kind permission of the Editor and Publishers of MIMS (*Monthly Index of Medical Specialities*).

### INTERACTIONS WITH SULPHONYLUREAS (based on Reynolds (1))

Many compounds have been reported to interact with sulphonylureas. Most are due to either displacement of the sulphonylurea from plasma proteins or to alterations in their metabolism or excretion (2). Many of the reports involve the older sulphonylureas such as chlorpropamide or tolbutamide. Reports may be categorized into two classes:

- (i) interactions which may diminish the hypoglycaemic effect; and
  - (ii) interactions which may increase the hypoglycaemic effect.
- 
- (i) Compounds that may diminish the hypoglycaemic effect and thus necessitate an increase in the dosage requirements of sulphonylureas include: rifampicin (3) and the thiazide diuretics (4). There is also a theoretical risk of a diminished hypoglycaemic effect with adrenaline, aminoglutethimide, chlorpromazine, corticosteroids, cyclophosphamide, diazoxide, gemfibrozil, isoniazid, oestrogens, oral contraceptives, phenytoin and thyroid hormones.



(prb)-produced from proinsulin synthesised by bacteria using recombinant DNA technology

(pyr)-produced from a precursor synthesised by yeast using recombinant DNA technology

\*Speed of onset is proportional to amount of soluble insulin Key: V = vial. P = pre-filled pen. C = cartridge. C<sub>1</sub> = compatible with reusable pens Autopen; NovoPen, II, Classic, Fun. C<sub>2</sub> = compatible with reusable pens Autopen; BD pen; Diaper. C<sub>3</sub> = compatible with reusable pens BD pen +. Pen needles: BD Microfine + 12mm, BD Microfine + 8mm (short), NovoFine 8mm (short) and NovoFine 12mm compatible with all pre-filled and reusable pens except Diaper (short needles not compatible). N.B: Reusable pens and needles NOT prescribable at NHS expense.

(emp)-produced by enzymatic modification of porcine insulin (insulin lispro)-human insulin analogue, rDNA origin

(ii) Compounds that may increase the hypoglycaemic effect of sulphonylureas and necessitate a reduction in their dosage include: anti-infective agents such as chloramphenicol (5), fluconazole (6), ketoconazole (7) miconazole (8), sulphonamides (9) including co-trimoxazole (10, 11); some anti-inflammatory agents and analgesics, including azapropazone (12), indobufen (13), phenylbutazone (14), and salicylates (15); also coumarin anticoagulants (16) and heparin (17); lipid-regulating agents such as clofibrate (18), halfenate (19) and monoamine oxidase inhibitors (20). Other compounds that may be implicated in such interactions include: captopril (21, 22), cimetidine (23), doxepin (24), enalapril (22, 25), fenfluramine (26), methyldopa (27), nortriptyline (24), probenecid, ranitidine (28) and sulphapyrazone (29). There is also a theoretical risk of increased hypoglycaemic effects with anabolic steroids, cyclophosphamide, isoniazid, mebendazole, octreotide, and tetracyclines.  $\beta$ -Blockers may mask some of the sympathetic warning signs of hypoglycaemia, they may have hypoglycaemic or hyperglycaemic actions of their own (30) and there have been reports that they reduce the hypoglycaemic action of glibenclamide (31). Reports of the effect of calcium-channel blockers on glucose tolerance are conflicting; any overall effect is probably marginal (30). Reports of the more important of these individual interactions are described below. Most of these refer to the older sulphonylureas, chlorpropamide or tolbutamide, but the possibility of similar interaction with more recently developed antidiabetic agents should be borne in mind.

A review of 1418 cases of drug-induced hypoglycaemia reported since 1940 has shown that the sulphonylureas (especially chlorpropamide and glibenclamide), either alone or with a second hypoglycaemic or potentiating agent, account for 63% of all cases (32).

#### **INTERACTIONS WITH INSULIN (based on Reynolds (1))**

The lists of drugs that have an effect on blood glucose concentrations and may alter the insulin requirements are similar to those which affect the sulphonylureas and other antidiabetic agents.

- (i) Those drugs with hypoglycaemic activity which may decrease insulin requirements are: anabolic steroids, aspirin, fenfluramine, monoamine oxidase inhibitors and octreotide. There have also been isolated reports of decreased insulin requirements with captopril (35), clofibrate, enalapril (36), guanethidine (37), mebendazole (38) and oxytetracycline (39). Gemfibrozil, as with the clofibrate group, may improve glucose tolerance and have additive effects if given with antidiabetic agents (41).
- (ii) Increased requirements of insulin may occur with: adrenaline, chlorpromazine, oral contraceptives, thiazide diuretics and thyroid hormones. There have been isolated reports of increased insulin requirements or aggravation of hyperglycaemia with chlordiazepoxide (40), diltiazem (41) and dobutamine (42).

The following drugs may increase or decrease insulin requirements: alcohol,  $\beta$ -

blockers, cyclophosphamide (42, 43) and isoniazid (44).  $\beta$ -Blockers may also mask some of the prodromal adrenergic signs of insulin-induced hypoglycaemia.

Details of some of these interactions are summarized in the following Table of Drug Interactions.

<i>Combination</i>	<i>Interaction</i>
<b>Antidiabetic agent/ acarbose</b>	Acarbose is an inhibitor of $\alpha$ -glucosidase and retards the absorption and digestion of carbohydrates in the small intestine, and hence, reduces the increase in blood glucose concentrations after a carbohydrate load. It may potentiate the effects of other hypoglycaemic agents, including insulin, and may necessitate a reduction in their dosage. Concomitant administration of gastrointestinal adsorbents and digestive enzyme preparations may diminish the effects of acarbose and should be avoided. Neomycin and cholestyramine may enhance the effects of acarbose and a reduction in its dosage may be required (45–49).
<b>Antidiabetic agent/ alcohol</b>	Large intakes of alcohol may cause severe hypoglycaemia (50–52). In general diabetic patients do not need to abstain from alcohol but they should not exceed 3 units/day (males) or 2 units/day (woman) (53). However, patients need to take account of the calorific value of alcohol, including any sugar-containing mixes in the management of their diet (54).
<b>Biguanides</b>	In patients on metformin, binge-drinking increases the risk of lactic acidosis by potentiating the effects of metformin on lactate metabolism (55–57).
<b>Sulphonylureas</b>	In alcoholics there is induction of hepatic microsomal enzymes and a reduced half-life of, for example, chlorpropamide and tolbutamide (58, 59). In heavy drinkers (30 units/day) blood levels of tolbutamide are roughly halved (58). Blood clearance of tolbutamide in those who drink only a few times per week, or in ex-drinkers with advanced, but well compensated cirrhosis of the liver is not normally affected (60). Most patients with diabetes need not abstain from alcohol (54). Chlorpropamide facial flush (CPAF) has been

*Combination**Interaction*

suggested as a marker for a special type of non-insulin-dependent diabetes and may be akin to metencephalin-induced flush. A central prostaglandin-dependent step in CPAF is proposed and blockade by aspirin is thought to be due to interference with prostaglandin synthesis (52, 61–70). Facial flushing occurred in two of 43 insulin diabetics treated with tolbutamide (71).

**Antidiabetic agent/  
anabolic steroid**

Insulin requirements may be reduced; the hypoglycaemic response to tolbutamide may be enhanced (72). This combination should be avoided, it is doubtful if there is any useful role for anabolic steroids in diabetic patients.

**Antidiabetic agent/  
antimicrobial agent  
Chloramphenicol**

Chloramphenicol (2 g/day for 10 days) has been shown to increase the half-life of tolbutamide three-fold. Similarly chloramphenicol (1.5–3 g/day) increased the half-life of chlorpropamide to 40–146 hr compared with the normal figures of 30–36 hr (50, 51).

**Co-trimoxazole**

A 69-year-old diabetic woman taking chlorpropamide 500 mg/day was hospitalized with hypoglycaemia and associated neurological symptoms 2 days after starting co-trimoxazole (two tablets, twice daily). It was thought that the sulphamethoxazole component of the co-trimoxazole either displaced chlorpropamide from its protein binding sites or competed for renal excretion (73, 74). A similar case has been reported in which glipizide and co-trimoxazole drastically lowered blood glucose levels to 2.2 mmol/l in a hospitalized patient; this hypoglycaemia was accompanied by a severely changed mental status requiring stoppage of glipizide. The patient retained glycaemic control when the course of co-trimoxazole ceased (74).

Antibacterials other than sulphonamides are preferred in patients on chlorpropamide or any other sulphonylurea, but if they are essential then a possible reduction of the dose of the antidiabetic drug and careful monitoring of glycaemic control may be an alternative.

**Isoniazid**

Glycosuria and hyperglycaemia have been reported with a sulphonylurea/isoniazid combination. Two cases

<i>Combination</i>	<i>Interaction</i>
<b>Isoniazid cont.</b>	of irreversible diabetes caused by isoniazid have been reported (75). Choice of an alternative tuberculostatic drug is recommended.
<b>Tetracycline</b>	Phenformin-induced lactic acidosis has been reported to be precipitated by tetracyclines (76, 77). The mechanism of this interaction is unknown but it is more likely to occur if there is concomitant renal impairment. Phenformin has been withdrawn from clinical use in the UK and many other countries due to its association with lactic acidosis.
<b>Antidiabetic agent/ anticoagulant coumarins</b>	Dicoumarol and other coumarin anticoagulants may increase the half-life of tolbutamide in both diabetics (16, 78) and normal subjects (79). A similar effect has been described with chlorpropamide (80). There have been a few early instances of tolbutamide enhancing the activity of dicoumarol (81). This effect has not been reported in later studies involving dicoumarol (81–83), warfarin (82) and phenprocoumon (84), although one study did demonstrate altered dicoumarol pharmacokinetics (83). An absence of effect has been documented for phenprocoumon and insulin, glibencamide or glibornuride (84). Metformin has been reported to diminish the activity of phenprocoumon (85). A woman maintained on warfarin for over 30 years was started on glibencamide (10 mg daily). Forty-eight hours later she reported bruising around the left shoulder and upper arm which later spread to the soft tissue of her chest wall tracking down towards the abdomen. Her internationalized normalized ratio was 6.6 (it was 2.3 before glibenclamide). Warfarin was stopped and she was given fresh plasma. Despite further transfusions her coagulation remained abnormal (INR 5.2). Glibenclamide was stopped and within 24 hr her INR returned to normal (2.2) (86). Although interactions between sulphonylureas and warfarin have been recognized since 1970, these applied largely to chlorpropamide. All combinations of a sulphonylurea and anticoagulant should be used with extreme

<i>Combination</i>	<i>Interaction</i>
	caution; a reduction in the dose of the sulphonylurea should be anticipated.
<b>Heparin</b>	A 64-year-old diabetic stabilized on glipizide was given a heparin intravenous infusion. He suffered recurring hypoglycaemic attacks over 4 days. Sulphonylureas are highly bound to protein, and even small doses of heparin indirectly decrease the binding of drugs by increasing free fatty acid concentrations – an effect more pronounced in diabetics than others (73, 87). Anticipate this interaction and avoid this combination if possible.
<b>Antidiabetic agent/ antidepressant (MAOIs)</b>	MAOI antidepressants enhance or prolong the hypoglycaemic responses to both insulin and the sulphonylureas. It is not known whether other classes of antidiabetic drugs (e.g. metformin and glymidine) are similarly affected, although this is a possibility since it is thought that MAOIs interfere with the compensatory adrenergic response to hypoglycaemia releasing glucose from liver glycogen (88). The normal adrenergic response to hypoglycaemia (sweating and shaking) is not affected (89). This combination should be avoided.
<b>Antidiabetic agent/ anti-fungal ketoconazole fluconazole</b>	Clearance of tolbutamide was significantly decreased by concomitant administration of ketoconazole resulting in mild hypoglycaemia in five of seven healthy subjects (90). Diabetics stabilized on tolbutamide should be monitored for altered glycaemic response if ketoconazole is initiated or discontinued. Fluconazole has also been noted to increase the AUC of tolbutamide (91). The effects of other antifungal agents on tolbutamide are unknown.
<b>Antidiabetic agent/ anti-hypertensive</b>	Hypertension, congestive heart failure and myocardial infarction are common problems among diabetics. Many of these disorders necessitate drug treatment of long duration. A complicating factor in such treatments is the adverse effect on glucose metabolism of many drugs including thiazide diuretics and $\beta$ -blocking agents.

<i>Combination</i>	<i>Interaction</i>
<b>ACE inhibitors</b>	<p>Angiotensin-converting enzyme (ACE) inhibitors are now the usual treatment for cardiovascular disorders of diabetics since they are effective and have few adverse effects. There have, however, been several reports of hypoglycaemia associated with their use (21, 22, 33, 92). Most cases have been in non-insulin-dependent diabetics treated with captopril or enalapril. Several clinical studies with small and selected groups of patients have been done, but they have not resolved the question of whether ACE inhibitors precipitate hypoglycaemia (93–96). More recent evidence has suggested that hypoglycaemia was significantly associated with the use of ACE inhibitors (odds ratio 2.8), and that this use was significantly associated with an increased risk of hospital admission for hypoglycaemia both among users of insulin (odds ratio 2.8) and oral antidiabetic drugs (odds ratio 4.1). A significantly increased risk of hypoglycaemia was observed with the use of captopril (97) and the authors thought that this risk of hypoglycaemia should be taken into account when treating diabetics. A further recent paper showed that enalapril given over 4 weeks improved insulin sensitivity by increasing glucose storage in hypertensive patients with non-insulin-dependent diabetes (98). The bulk of evidence supports the view that an ACE inhibitor is the primary antihypertensive agent of choice for diabetic patients.</p>
<b>Diazoxide</b>	<p>Diazoxide was the outcome of research to separate the antihypertensive and diuretic actions of the thiazides. Diazoxide has retained all the hyperglycaemic actions of the thiazides. It inhibits insulin secretion in response to glucose load. In one series, half the number of hypertensive patients treated with diazoxide developed glycosuria (99).</p>
<b><math>\beta</math>-blocker</b>	<p><math>\beta</math>-blockers may mask some of the prodromal signs of hypoglycaemia mediated by adrenergic mechanisms, notably shaking and sweating, by which diabetics and their relatives recognize the onset of a hypoglycaemic attack (89). They have been associated with both</p>

*Combination**Interaction*

hyperglycaemia (100, 101) and diabetes mellitus (102) and also hypoglycaemia (30, 32).

Other effects include inhibition of endogenous insulin secretory response to glucose or sulphonylurea and impaired peripheral circulation (see review (103)).

**Metoprolol**

Cardioselective  $\beta$ -blockade with metoprolol reduced blood pressure satisfactorily in a group of insulin-independent diabetics without influencing glycaemic control or recognition of hypoglycaemia (104). Other studies in type 2 diabetics have confirmed that the use of a selective  $\beta$ -blocker (acebutolol) has advantage over a non-selective agent (propranolol) (105).

**Propranolol**

Propranolol precipitation of hypoglycaemia in insulin-dependent diabetics was first noted in the 1960s. In a review of drug-induced hypoglycaemia, 49 cases of severe hypoglycaemia were identified with non-selective  $\beta$ -blockers (32). The optimal  $\beta$ -blocker for use in type 2 diabetic patients appears to be a  $\beta_1$ -cardioselective agent with little or no lipophilicity (30). The most likely mechanism involved in this interaction is blockade of glucose release from liver glycogen stores.

**Clonidine**

The effects of clonidine on carbohydrate metabolism are variable. Studies show that it does not affect carbohydrate metabolism in diabetics (106) or non-diabetic hypertensive patients (107). However, clonidine was associated with elevated fasting blood sugar levels in one patient (108), while another study in 10 diabetic hypertensive patients showed that clonidine impaired the response to an acute glucose load but did not significantly affect diabetics over a 10-week period (109). Severe postural hypotension (110) and paradoxical hypertension (111) have been reported following clonidine administration to diabetics with autonomic neuropathy.

**Ca<sup>+</sup> channel blocker nifedipine**

There is growing evidence that the calcium channel blocker, nifedipine, may interfere with the glycaemic control of diabetic patients being treated with insulin or oral hypoglycaemic agents. Nifedipine 600 mg daily

*Combination**Interaction***Ca<sup>+</sup> channel blocker  
nifedipine cont.**

caused glucose intolerance in normal subjects and delayed the insulin response to oral glucose in non-insulin-dependent diabetics (112). Another study showed impairment of glucose tolerance in non-insulin-dependent diabetics after receiving nifedipine 30 mg daily for 10 days (113). Other reports on interference with glycaemic control have been made in several studies (114–120), nifedipine has been associated with most of these reports, although diltiazem and verapamil have been implicated as well (117, 120). In contrast, other groups found no change in glucose tolerance in diabetics and non-diabetic subjects who took nifedipine 20–40 mg daily (122–132).

The possible mechanism of this interaction allows much speculation. It has been suggested (120) that a change in intracellular calcium may lead to an alteration in insulin secretion or to an increased peripheral insulin resistance. The latter may result from counter regulatory secretion (glucagon, catecholamines, glucocorticoids or growth hormone) or from altered enzymatic reactions that modify glucose production and use.

The validity of this interaction is uncertain and until more evidence is available it would be prudent for all diabetic patients receiving antihypertensive treatment with nifedipine or other calcium channel blocker to be regularly monitored for continuation of good glycaemic control. If glycaemic control is impaired then alternative antihypertensive therapy should be considered.

**Antidiabetic agent/  
aspirin and salicylates**

*In vitro* studies have shown that aspirin and salicylates displace tolbutamide and chlorpropamide from plasma binding thus increasing unbound active sulphonylurea (133). Overdosage with salicylates can produce hypoglycaemia in children. Although it is recognized that therapeutic doses of salicylates in adults can lower blood glucose concentrations in diabetic and non-diabetic subjects alike, opinion on the clinical significance of this effect varies (32, 134). Salicylates have been implicated in a few cases of hypoglycaemia

*Combination**Interaction*

in adults (15, 32) and some of these suggest that patients with renal failure or those receiving high doses in rheumatoid arthritis may be at risk (134).

Hypoglycaemia has been reported in one patient with renal failure following excessive application of a topical preparation containing salicylic acid (135).

The insulin requirement of diabetics can be reduced by aspirin; in one series of 14 patients, salicylate plasma levels of 34–45 mg/100 ml reduced the daily insulin zinc suspension requirements by up to 48 units (136). Cases have also been reported where aspirin has contributed to profound hypoglycaemia in patients on sulphonylureas (137, 138). However, interactions with aspirin and salicylates seem to be rare and only occur with high and continuous dosage. Normal dosage of aspirin is unlikely to have any appreciable effect on glycaemic control of diabetics.

**Non-steroidal anti-inflammatory agents**

Some non-steroidal anti-inflammatory agents, including azapropazone (12), fenclofenac (139), indobufen (13), and phenylbutazone (140–142), will increase the hypoglycaemic effect of sulphonylureas. Glycaemic control may be difficult and should be monitored. Severe hypoglycaemic episodes have been reported (12, 141, 142). A reduction in dosage of the NSAID may be necessary. Most of these interactions are due either to displacement of the sulphonylurea from plasma protein binding or to alterations in the metabolism and excretion of the sulphonylurea (2).

**Antidiabetic agent/  
cimetidine metformin**

Cimetidine administration resulted in increased plasma metformin concentrations in seven healthy subjects. The renal clearance of metformin was reduced due to competition for proximal tubular secretion. A reduction in metformin dosage may be required in patients taking this combination to avoid the risk of lactic acidosis (143).

**Antidiabetic agent/  
clofibrate**

The interaction is complex since clofibrate has been shown to alter glucose tolerance in both diabetic and non-diabetic patients. Clofibrate (2 g/day) caused hypoglycaemia in four of 13 diabetic patients treated

<i>Combination</i>	<i>Interaction</i>
<b>Antidiabetic agent/ clofibrate cont.</b>	with various sulphonylureas. The patients who demonstrated this effect had abnormally low plasma albumin levels; it is possible that this interaction took place at plasma binding levels (144). This combination should be avoided unless the patient is monitored during the first week of taking the combination. The dosage of the antidiabetic agent may need adjusting during concomitant therapy (145).
<b>Antidiabetic agent/diuretic chlorthalidone ethacrynic acid frusemide thiazides triamterene</b>	Diuretics tend to elevate the blood sugar level in diabetics and prediabetics. Thiazides and chlorthalidone antagonize the action of antidiabetic drugs particularly the sulphonylureas. The mechanism of interaction is uncertain but it is believed that K <sup>+</sup> loss induced by some diuretics may be partially responsible (146). Patients should be monitored for diabetic control and, If necessary, a less diabetogenic diuretic (e.g. indapamide) should be substituted.
<b>Acetazolamide</b>	Acetazolamide has been reported to cause symptomatic metabolic acidosis in the elderly and in diabetic patients. It should be given with care to diabetics and they should have urea and electrolyte concentrations measured before and during treatment with acetazolamide (147–150).
<b>Amiloride</b>	Elderly diabetic patients are at particular risk of developing hyperkalaemia when treated with this diuretic (151).
<b>Antidiabetic agent/ Karela</b>	Karela ( <i>Momordica charantia</i> ) a component of Indian curry has been anecdotally related to one case of potentiation of hypoglycaemic effects of chlorpropamide. It is used by Asian immigrants in the UK to treat diabetes (152).
<b>Antidiabetic agent/oral contraceptive</b>	The potential effects of oral contraceptives on glucose tolerance are of particular concern because of the risk that impaired glucose tolerance will exacerbate their cardiovascular effects (153). Early studies suggested that that the prevalence of abnormal glucose tolerance in oral contraceptive users was increased from about 4 to 35%, but subsequent studies produced conflicting

*Combination**Interaction*

results. The decrease in glucose tolerance depends not only on the oestrogen dose but also on the type of progestogen. Levonorgestrel has been reported to be the most potent progestogen in reducing glucose tolerance (154). Subsequent studies have suggested that glucose tolerance testing may not be the best way of assessing the effects of oral contraceptive on carbohydrate metabolism (155). Insulin and C-peptide production was measured and it was shown that although levonorgestrel-containing combined preparations had a greater effect on glucose tolerance, desogestrel- or norethindrone-containing preparations produced a similar degree of insulin resistance, suggesting that this depends on the oestrogenic component, and is modified by the progestogen (155). Oral contraceptives do appear to increase the subsequent risk of developing type 2 diabetes (156), and they increase the insulin requirements of diabetics (157, 158). The use of other methods of contraception should be considered for diabetic patients, if this is not practicable, patients should be checked more closely for decreased diabetic control. Diabetogenic effects will depend on a number of factors including type and dose of oral contraceptive components, type of patient and duration of administration.

**Antidiabetic agent/  
smoking**

Studies in ketone-prone insulin-dependent diabetics have shown an average decrease of 113% in insulin absorption in the first 30 min after smoking (159). Previous studies have shown that diabetic smokers need on average 10–20% more insulin than non-smokers. This percentage increases to 30% in heavy smokers (160). Diabetic patients should be advised to stop smoking.

**Antidiabetic agent/  
sulphinpyrazone**

Sulphinpyrazone can displace sulphonylureas from plasma protein binding, and may possibly increase their activity. Co-administration of sulphinpyrazone (200 mg, 6-hourly) and tolbutamide (500 mg i.v. over 10 min) reduced mean plasma and prolonged tolbutamide by 40% and prolonged its mean half-life by 80% (161). Avoid this combination; it would be

*Combination**Interaction*

**Antidiabetic agent/  
sulphonylurea cont.** prudent to anticipate the same interaction with other sulphonylureas.

**Antidiabetic agent/  
sympathomimetic  
ritodrine** Care is required when sympathomimetic agents are given to diabetics. Ritodrine, a direct-acting sympathomimetic with predominantly  $\beta$ -adrenergic activity was given by i.v. infusion to delay contractions in preterm labour. Hyperglycaemia (21.5 mmol/l) and ketoacidosis resulted. The patient delivered a stillborn baby (162). As diabetics do not have an adequate insulin response to handle  $\beta$ -adrenergic-induced hyperglycaemia, there is a danger that metabolic acidosis may occur.

**Antidiabetic agent/  
thyroid hormones** As thyroid status influences metabolic activity and most body systems, correction of hypothyroidism with thyroid hormones may affect other disease states and their treatment. The initiation of thyroid replacement therapy may increase insulin or oral hypoglycaemic requirements (163, 164).

**Insulin/glass and plastics** The adsorption of insulin onto glass and plastics used in administration sets has been decreased by the addition of albumin or polygeline to insulin solutions. Some workers consider this to be unnecessary since in practice insulin adsorption is not a major problem (165, 166). Running approximately 10 ml of the insulin solution through the intravenous tubing before beginning the infusion has been suggested by some (166). See also Chapter 13 Interactions with Medicinal Plastics.

**Insulin/glucagon** Glucagon is injected in the treatment of insulin-induced hypoglycaemia when administration of i.v. glucose is not possible. Intranasal preparations are being developed. Supplementary carbohydrate should be given once the patient has responded to prevent secondary hypoglycaemia (167). This agent is also used in the treatment of  $\beta$ -blocker poisoning (168).

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## **6.2 INTERACTIONS WITH CORTICOSTEROIDS**

### **CORTICOSTEROIDS WITH MAJOR GLUCOCORTICOID EFFECTS**

<b>Beclomethasone dipropionate</b>	<b>Fluprednisolone</b>
<b>Betamethasone</b>	<b>Hydrocortisone (cortisol)</b>
<b>Budesonide</b>	<b>Medrysone</b>
<b>Ciclomethasone</b>	<b>Meprednisone</b>
<b>Cortisone acetate</b>	<b>Methylprednisolone</b>
<b>Cortivazol</b>	<b>Paramethasone acetate</b>
<b>Deflazacort</b>	<b>Prednisolone</b>
<b>Dexamethasone</b>	<b>Prednisone</b>
<b>Flumethasone pivalate</b>	<b>Prednylidene</b>
<b>Flunisolide</b>	<b>Tixocortol pivalate</b>
<b>Fluoromethalone acetate</b>	<b>Triamcinolone</b>

### **CORTICOSTEROIDS WITH MAJOR MINERALOCORTICOID EFFECTS**

<b>Aldosterone</b>
<b>Deoxycortone acetate</b>
<b>Fludrocortisone acetate</b>

### **INTRODUCTION**

The spectrum of drug-drug interactions involving corticosteroids is limited and the mechanisms involved are largely well understood. For example, glucocorticoids (see above list) can induce cytochromes P450 CYP3A3, 3A4, 3A5, and 3A7, and may compete for metabolism with a number of drug substances including cyclosporin, erythromycin, lidocaine, midazolam, nifedipine, quinidine and warfarin, which are metabolized by the same enzyme system (1). It is not surprising, therefore, that interactions between some of these drugs and individual corticosteroids have been reported in the clinic.

The pharmacokinetics of corticosteroids can be modified by concomitant use of P450-inducing agents (e.g. phenytoin or rifampicin) or P450-inhibiting drugs (e.g. cimetidine) and these interactions are largely predictable. The glucocorticoid action of corticosteroids will influence the actions of insulin and oral hypoglycaemics.

The mineralocorticoids (see above list) are rarely used, exceptions include the treatment of primary adrenal insufficiency, in which both mineralocorticoid and glucocorticoid replacement is necessary. Mineralocorticoids can, by  $\text{Na}^+$  and water

retention, reduce the effects of hypotensives and greatly influence the adverse effects of concomitant diuretics or other potassium-losing drugs. These effects may underlie significant clinical interactions. Many of these interactions were discovered during the early use of corticosteroids and are now well recognized. Generally, such interactions do not occur with inhaled corticosteroids or topical preparations unless dosage is high and prolonged. Interactions are largely confined to oral or systemically administered steroids. A recent review has summarized the adverse effects of corticosteroids and their interactions in man (2).

The Table of Drug Interactions summarizes some of these established interactions.

<i>Combination</i>	<i>Interaction</i>
<b>Corticosteroids/ anticoagulants</b>	Corticosteroids may potentiate the effects of warfarin and can induce gastric ulceration with dangerous haemorrhage in anticoagulated patients (3). Ulceration may go unnoticed due to the euphoric effects of corticosteroids.
<b>Corticosteroids/ antidiabetics</b>	Antagonism of hypoglycaemic effects. Corticosteroids have intrinsic hyperglycaemic activity and may induce diabetes mellitus or may upset the established control of the diabetic patient (4, 5).
<b>Corticosteroids/ anti-emetics</b>	Dexamethasone makes a significant contribution to the efficacy of ondansetron in the control of acute cisplatin-induced emesis (6).
<b>Corticosteroids/ anti-epileptics</b>	Carbamazepine, phenobarbitone, phenytoin and primidone are all hepatic P450 enzyme inducers and will accelerate the metabolism of corticosteroids and reduce their effects (7–9).
<b>Corticosteroids/ antihypertensives</b>	The mineralocorticoid effects of corticosteroids, $\text{Na}^+$ and water retention may antagonize the effects of concomitant hypotensive therapy (10).
<b>Corticosteroids/aspirin</b>	Corticosteroids decrease the blood salicylate concentration by increasing the glomerular filtration rate. Decreasing corticosteroid dosage in patients on aspirin may result in increased serum salicylate levels with the possibility of salicylism (11). Corticosteroids and aspirin are both ulcerogenic (12).

<i>Combination</i>	<i>Interaction</i>
<b>Corticosteroids/bile acid-binding resins</b>	Colestipol causes a significant impairment of oral hydrocortisone absorption (13).
<b>Corticosteroids/cardiac glycosides</b>	Hypokalaemia due to corticosteroids potentiates the effect of cardiac glycosides (14).
<b>Corticosteroids/chlorpromazine</b>	Chlorpromazine reduces gut motility and may enhance the absorption of oral corticosteroids (15).
<b>Corticosteroids/cyclosporin</b>	A mutual inhibition of metabolism occurs between cyclosporin and corticosteroids increasing the plasma concentration of both agents (16). Increased plasma cyclosporin levels increase the danger of nephrotoxicity (17–22).
<b>Corticosteroids/diuretics</b>	Mineralocorticoids promote Na <sup>+</sup> and water retention and antagonize diuretic effects; acetazolamide, frusemide, other loop diuretics and thiazides increase the risk of hypokalaemia. Potassium-losing diuretics given together with corticosteroids may produce serious hypokalaemia (10).
<b>Corticosteroids/contraceptives</b>	Oestrogens enhance the anti-inflammatory action of corticosteroids and retard the metabolism of cortisol possibly by its increased binding to globulin (23). Contraceptive failure has been reported in women using intra-uterine devices and taking corticosteroids (24). There have been several reports of an enhanced effect of corticosteroids in women receiving oestrogens or taking oral contraceptives, the dose of corticosteroid may need to be reduced (24, 25).
<b>Corticosteroids/rifampicin</b>	Rifampicin is a potent inducer of cytochrome P450; it accelerates the metabolism of corticosteroids and reduces their clinical efficacy (26). Acute adrenal crisis has been precipitated by rifampicin in patients with adrenal insufficiency (27), and induction of microsomal enzyme systems may be enough to compromise even patients with mildly impaired cortisol production. Critical hypotension has

<i>Combination</i>	<i>Interaction</i>
<b>Corticosteroids/ rifampicin cont.</b>	also developed in non-Addisonian patients within 7–10 days of starting rifampicin therapy (28). Rifampicin reduces the half-life of cortisol and steroid requirements are increased four-fold in Addison's disease (29). Antitubercular rifampicin therapy in patients with renal transplants caused increased metabolism of corticosteroids and onset of signs of graft rejection (30). Treatment of nephrotic syndrome by prednisolone in a child also receiving rifampicin plus isoniazid failed and then improved when the two antitubercular agents were stopped (31, 32). The plasma clearance of prednisolone increased by 45% when rifampicin was given (32) and prednisolone dosage had to be increased by 93% when asthmatic patients also took rifampicin (33).
<b>Corticosteroids/ <math>\beta_2</math>-sympathomimetics</b>	Corticosteroids in high dosage increase the risk of hypokalaemia with high doses of bambuterol, eformoterol, fenoterol, pirbuterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, terbutaline and tulobuterol (34).
<b>Corticosteroids/ ulcer-healing drugs</b>	Concomitant administration of corticosteroids, especially mineralocorticoids with carbenoxolone, increases the risk of hypokalaemia. Pseudoaldosteronism is a possible risk of therapy with carbenoxolone (35).

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## **6.3 INTERACTIONS WITH DRUGS USED IN THE TREATMENT AND PREVENTION OF OSTEOPOROSIS**

Four main groups and one subsidiary group of substances are used in the treatment and prevention of osteoporosis.

**Firstly**, oestrogens: these may or may not be administered in combination with progestogens for post-menopausal hormone replacement therapy or long term in the prevention of osteoporosis.

The most widely prescribed products in this group are those containing conjugated oestrogens derived from pregnant mares' urine and may be taken in doses of 0.625, 1.25 or 2.5 mg without or with norgestrel 0.15 mg Premarin or Prempak C, respectively.

All oral preparations of oestrogen are subject to first pass metabolism in the intestine and liver. Therefore formulations of oestrogen in subcutaneous implants or dermal patches have been developed for use in hormone replacement therapy (HRT).

**Secondly**, male sex hormones are being used in the treatment of recently recognized age-related male osteoporosis.

**Thirdly**, the calcitonins, of which pork, eel, salmon and synthetic human calcitonins are used therapeutically. The calcitonins are polypeptide hormones of molecular weight of about 3500, involved in the regulation of calcium and bone metabolism. They all have the property of lowering plasma calcium by diminishing the rate of bone resorption by inhibition of osteoclast activity. They are used in Paget's disease of bone, hypercalcaemia in malignant disease, and salmon calcitonin has been used intranasally in post-menopausal osteoporosis (1, 2) and in children with osteoporosis associated with nephrosis (3).

Synthetic salmon calcitonin is more potent than porcine calcitonin and is weight for weight more potent than the other calcitonins. In the high doses of salmon calcitonin used in the treatment of Paget's disease of bone it has a rapid and profound pain-releasing action which is too rapid to be due entirely to its effects on bone resorption.

A number of hypotheses have been proposed to account for the analgesic effect of calcitonin. Current thinking is that this is due to the involvement of the endogen-

ous opioid system. Plasma concentrations of  $\beta$ -endorphin has been shown to rise after intranasal administration of calcitonin in healthy subjects (4).

Corticosteroid-induced osteoporosis may respond to calcitonin treatment (5). Side effects of calcitonin therapy are nausea, vomiting, flushing, tingling of the hands and unpleasant taste. Local reactions of injection site have been reported.

**Fourthly**, the bisphosphonates, disodium etidronate, disodium pamidronate, sodium clodronate, tiludronate. Bisphosphonates are absorbed onto hydroxyapatite crystals, so slowing both their rate of growth and dissolution, and reducing the rate of bone turnover.

Prolonged treatment of osteoporosis with etidronate in excess of 4 years has been shown on bone biopsy to lead to an excess of peritrabecular fibrosis and histologically defined mild to moderate osteomalacia. Osteoid, which may accumulate at high doses of continuous etidronate therapy, is able to be mineralized normally after discontinuation of therapy.

Hyperphosphataemia has been observed in patients on bisphosphonate therapy and is apparently due to a drug-related increase in renal tubular reabsorption of phosphate. It is not usually grounds for discontinuing therapy. Serum phosphate levels return to normal 2–4 weeks after discontinuing therapy.

Side effects of bisphosphonates are mainly gastrointestinal, involving diarrhoea, abdominal pain, constipation, nausea, vomiting. Dermatological hypersensitivity reactions have been reported. There have been rare reports of leucopenia, agranulocytosis and pancytopenia. Mild leg cramps occur in 5% of patients on etidronate. Peripheral neuropathy has also been recorded.

**Finally**, sodium fluoride is the only bone formation-stimulating drug that has been widely tested. In two major, adequately controlled clinical trials, fluoride at a dosage of 75 mg/day substantially increased bone mass but did not significantly decrease the rate of vertebral fractures. Preliminary results with use of a lower dosage (50 mg/day) in a delayed-release variant indicated a decrease in the rate of vertebral fractures. These early results, however, must be confirmed, and the therapeutic window of fluoride will likely be small. Furthermore, direct studies of bone from patients treated with a dosage of 50 mg/day indicate increased fragility of the fluoride-treated bone. Thus the future role of sodium fluoride in the treatment of osteoporosis is currently unclear. The use of sodium fluoride in osteoporosis has been reviewed by Khasla and Riggs (6).

## DRUG INTERACTIONS

Drug interactions with oestrogens used in the treatment of osteoporosis are dealt with in the specific chapter on oestrogens and progestogens. There are no clinically relevant interactions with male sex hormones or calcitonin. Drug interactions with bisphosphonates are also not common. Articles in the literature contain specific warnings about the interactions between etidronate and vitamins or foods with a

mineral supplement or content. Materials with a high calcium content such as milk, may reduce the absorption of disodium etidronate. Vitamins with mineral supplements such as iron, calcium, laxatives containing magnesium, or antacids containing calcium or aluminium should not be taken within 2 hr of dosing with disodium etidronate. The elderly patient with osteoporosis may need special counselling to understand when to take calcium or iron supplements, which are often recommended to the elderly because of deficient dietary intake. Such restrictions may appear irrational to the elderly osteoporotic patient unless properly explained (13).

Other bisphosphonates used in the treatment of osteoporosis interact with food, mineral ions and vitamins with mineral supplements in the same way as disodium etidronate (7, 14–18). Fleish (17) cautioned that the absorption of bisphosphonates is diminished in the presence of calcium, and that bisphosphonates should not be given before meals and never together with milk products.

No interactions between any of the bisphosphonates and other drug therapies have been reported, other than the risk of development of severe hypocalcaemia when bisphosphonates are given concomitantly with aminoglycoside antibiotics (19). The warning about interactions between bisphosphonates and aminoglycoside antibiotics resulting in severe hypocalcaemia is given in the *British National Formulary* but is not given in any of the Data Sheets in the *ABPI Data Sheet Compendium* (1995–96) (20–22). However, the Data Sheet for disodium pamidronate does warn that pamidronate should not be co-administered with plicamycin (Mithramycin). Plicamycin lowers serum calcium and also blocks the hypercalcaemic action of vitamin D. It has been suggested that plicamycin may lower serum calcium levels by inhibiting the effect of parathyroid hormone on osteoclasts. Plicamycin inhibition of DNA-dependent RNA synthesis appear to render osteoclasts unable to fully respond to parathyroid hormone with the biosynthesis necessary for osteolysis.

## SYNERGISTIC EFFECTS

A few studies have been published which appear to indicate a synergistic action or additive effect between treatments (23–24). In one study, 6 months treatment with etidronate followed by 6 months treatment with calcitonin was considered to be of greater benefit than using the treatments the other way round (25). Rico *et al.* (26) on the basis of biochemical studies has claimed that calcitonin plus etidronate for 10 days a month produced more marked biochemical effects than the same regimen for 10 days followed sequentially by 20 days of etidronate.

In a 2-year study by MacIntyre *et al.* (27) it was shown that in a dose range of 2000–6000 IU of salmon calcitonin in post-menopausal women given with oestrogen + progestogen, there was an additive effect on bone mineral density over that achieved by calcitonin alone.

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# CHAPTER 7

## Drug Interactions with Oral Contraceptives

### INTRODUCTION (based on *British National Formulary* (1))

Oral contraceptives are divided into two main types: 'combined' which contain an oestrogen and a progestogen, and 'progestogen-only'. Hormonal preparations are also available for emergency contraception which are used after unprotected intercourse and before implantation of the fertilized egg in the uterus. Long-acting hormonal contraceptive preparations have been developed for subcutaneous implantation or depot intramuscular injection.

Many reports have been published on adverse reactions and interactions associated with the use of combined oral contraceptives. Much of this information involves older preparations containing higher doses of oestrogen and progestogen than are used currently.

### I. COMBINED

In this type an orally active progestogen (e.g. ethynodiol, levonorgestrel, norethisterone) is given in conjunction with an orally active oestrogen (e.g. ethinyloestradiol or mestranol). The oestrogen content ranges from 20 to 50 µg, and generally a preparation with the lowest oestrogen and progestogen content which gives good cycle control and minimal side-effects in the individual woman is chosen. Low strength preparations (containing 20 µg ethinyloestradiol) are particularly suitable for obese or older woman. Standard strength preparations (containing ethinyloestradiol 30 or 35 or 30/40 µg phased preparations) are appropriate for standard use in the case of those also containing ethynodrel, levonorgestrel or norethisterone. Phase preparations are more complex to take, but provide better cycle control than the equivalent 'monophasic' levonorgestrel or norethisterone formulations. High strength preparations (containing either ethinyloestradiol 50 µg or mestranol 50 µg)

provide greater contraceptive security but with an increased possibility of side effects. These are used mainly in the circumstances of reduced bioavailability.

#### **Advice from the Committee on Safety of Medicines**

The CSM has advised that results of studies on the safety of oral contraceptives in relation to venous thromboembolism have provided reassurance about thromboembolic risks associated with oral contraceptives containing levonorgestrel, norethisterone or ethynodiol (excess risk around five to ten cases per 100 000 women per annum) (2). The studies, however, indicated that combined oral contraceptives containing the newer progestogens, desogestrel and gestodene, are associated with around a two-fold increase in the risk. There is insufficient information to know whether there is any increased risk of thromboembolism associated with combined oral contraceptives containing norgestimate (3-7).

The CSM has advised that combined oral contraceptives containing gestodene and desogestrel should not be used by woman with risk factors for venous thromboembolism, including obesity, varicose veins, or a previous history of thromboembolism from any cause. Combined oral contraceptive preparations containing desogestrel or gestodene should only be used by women who are intolerant of other combined oral contraceptives, and are prepared to accept an increased risk of thromboembolism (2).

The timing and the means by which the CSMs advice was transmitted was initially criticized by some authorities but subsequent published evidence confirmed the CSMs concern (8).

## **II. PROGESTOGEN-ONLY**

With this type of contraception small doses of progestogen (ethynodiol diacetate, norethisterone, or levonorgestrel) have to be taken daily throughout the cycle in a continuous schedule. These preparations are less effective than the combined type oral contraceptives, and since their action appears to be short lived there tends to be a greater risk of pregnancy if tablets are missed. Oral progestogen-only preparations may offer a suitable alternative when oestrogens are contraindicated, but they have a higher failure rate than combined preparations. They are suitable for older women, for heavy smokers and for those with hypertension, valvular heart disease, diabetes mellitus or migraine. Menstrual irregularities (oligomenorrhoea, menorrhagia) are more common but tend to resolve on long-term treatment (1).

## **III. POST-COITAL (Emergency contraception)**

The hormonal method of emergency contraception is suitable for occasional use. It involves taking two tablets, each containing ethinyloestradiol 50 micrograms and levonorgestrel 250 µg, followed 12 hr later by a further two tablets. The method has only been established as effective if the first dose is taken within 72 hr of the

unprotected intercourse. It is less effective than insertion of an intrauterine device and should not be used as a routine method of contraception (1).

#### IV. A NEW DEVICE

A new contraceptive system (Persona, Unipath) has recently been launched in the UK. Persona tells a woman whether she is safe to have unprotected sexual intercourse without conceiving, by identifying her fertile period. The device consists of a small computerized monitor and disposable urine test sticks. The monitor displays a green light on the safe days and a red light when she is at risk of becoming pregnant. The test stick performs a dual immunochromatographic assay on: (i) oestrone-3-glucuronide (E3G), a major urinary metabolite of oestradiol, which peaks on average 24 hr before ovulation; (ii) luteinising hormone (LH), which surges around the time of ovulation and is used by the monitor to determine the end of the fertile period (current ovulation prediction tests detect this LH surge but do not measure E3G). In making its calculations the monitor notes the woman's own test stick readings, stores data about her cycle length, and data compiled from thousands of menstrual cycles (gained from Unipath studies and other literature). The device is claimed to be 93–95% reliable (9).

#### V. INTERACTIONS

Oral contraceptives may enhance or antagonize the pharmacological action of drugs used concurrently. Conversely, drugs that are inducers of P450 metabolic enzymes (e.g. carbamazepine, ethosuximide, griseofulvin, oxcarbamazepine, phenytoin, phenobarbitone, primidone, topiramate, and especially rifabutin and rifampicin) may augment metabolic degradation of the oral contraceptives and possibly reduce their efficacy.

Additional contraceptive precautions should be taken whilst taking the enzyme-inducing drug and for at least 7 days after stopping it. Note: rifampicin regularly results in menstrual irregularities and occasionally in unintended pregnancies. It is such a potent enzyme-inducing drug that an alternative method of contraception (such as an IUD) is always recommended. Even if a course of rifampicin lasts for less than 7 days, the additional contraceptive precautions should be continued for at least 4 weeks after stopping the rifampicin (1).

Menstrual irregularities and pregnancies have been reported (10) in women taking griseofulvin and oral contraceptives concurrently and more studies are required to confirm the validity of this interaction and the mechanism(s) involved.

Several cases of unintended pregnancy have been reported following the use of tetracyclines and there is sufficient evidence to warrant the use of other forms of contraception during the use of these antibiotics (11).

Some broad-spectrum antibiotics (e.g. ampicillin) may reduce the efficacy of combined oral contraceptives by impairing the bacterial flora responsible for recycling of ethinyloestradiol from the large bowel (12). Although up to 1985 there had

been 32 reports of unintended pregnancies in women receiving penicillins (25 of them with ampicillin) the ability of antibacterials to inhibit oral contraceptive efficacy remains controversial (12, 13). The evidence is, however, consistent with the supposition that efficacy is occasionally impaired. Some studies have pointed to interference with intestinal flora involved in enterohepatic circulation of oestrogens as being a likely mechanism for this interaction, and it would be prudent for women to take additional contraceptive precautions whilst taking a short course of a broad-spectrum antibiotic and for 7 days after stopping. If the course of antibiotics exceeds 2 weeks, resistance to this interference develops and additional precautions become unnecessary (1).

The efficacy of progestogen-only is not affected by broad-spectrum antibiotics but it is reduced by enzyme-inducing drugs (1).

Examples of actual or potentially clinically important interactions involving oral contraceptives are detailed in the following Table of Drug Interactions. For convenience this is divided into three parts: (i) those interactions which reduce contraceptive efficacy; (ii) interactions by which oral contraceptives modify the effects of concomitant medication, and (iii) those interactions which may potentiate the side effects of oral contraceptives.

### **1. Interactions which Reduce Oral Contraceptive Efficacy (See reviews 14–17)**

<i>Combination</i>	<i>Interaction</i>
<b>Oral contraceptive/ broad-spectrum antibiotic or antimicrobial agent</b>	Pregnancies were reported in women taking OCs who were also given ampicillin (18). Animal studies have shown that broad-spectrum antibiotics do reduce the enterohepatic circulation of OCs and these changes can be correlated with changes in the gastrointestinal flora (12). Reports of contraceptive failure in women given broad-spectrum antibiotics have been received by the Committee on Safety of Medicines in Britain (13).
<b>Ampicillin</b>	A study investigating the efficacy of an 8-day ampicillin treatment in seven women taking OCs failed to show any effect on plasma concentrations of ethinyloestradiol, levonorgestrel, norethisterone, FSH and progesterone when compared with control data from the same women (13). A further study on six women, each taking long-term OCs likewise failed to demonstrate any effect of ampicillin (given from days 9–16 of the contraceptive cycle) in any of the parameters measured in the first study (13). In spite of the early reports that ampicillin reduced the efficacy of OCs, this interaction has not been confirmed in control

<i>Combination</i>	<i>Interaction</i>
	studies. Possibly other factors (e.g. ampicillin-induced diarrhoea) may have been responsible for the apparent interaction.
<b>Griseofulvin</b>	By 1984, the Netherlands Centre for Monitoring of Adverse Reactions to Drugs and the British Committee on Safety of Medicines has received 22 reports of a possible interaction between griseofulvin and OCs (10). There were 15 cases of intermenstrual bleeding, five cases of amenorrhoea and two unintended pregnancies. The proposed mechanism of interaction is that griseofulvin induced liver enzymes which consequently lowered oestrogen concentrations to below effective levels. It should be noted that griseofulvin is embryotoxic and teratogenic in rats and that it is contraindicated in pregnancy. There have been anecdotal reports of contraceptive failure with fluconazole, itraconazole and ketoconazole. Additional contraceptive measures should be considered in women using both agents concurrently.
<b>Tetracyclines</b> (11) <b>Rifampicin</b> (20–23)	Available evidence suggest that other antibiotics (e.g. tetracyclines) may be associated with break-through bleeding or failure of contraception (e.g. rifampicin). Women taking low-dose oestrogen combined oral contraceptives should take extra precautions against conceiving in any cycle in which antibiotics are given. Increasing the dose of the combined-type oral contraceptive is not recommended since this will increase the dosage of oestrogen and increase the risk of a thromboembolic disorder.
<b>Oral contraceptive/anticonvulsant</b>	Oral contraceptive failure and breakthrough bleeding have been reported in numerous cases during periods of concurrent anti-epileptic therapy. Phenytoin, phenobarbitone, primidone, carbamazepine, oxcarbamazepine and ethosuximide have all been implicated. These drugs increase clearance of oral contraceptives by enzyme induction so decreasing their efficacy. OCs should be used with caution by women with a history of epilepsy. Of 41 epileptic women taking oral

*Combination**Interaction***Oral contraceptive/  
anticonvulsant *cont.***

contraceptives and phenytoin or phenobarbitone (or both) for a total of 955 months, three became pregnant. There were no pregnancies in the control group of 41 women taking OCs but not anticonvulsants for a total of 2278 months. Liver enzyme induction was incriminated in this interaction (24). Combined oral contraceptives may cause fluid retention and so precipitate seizures in epileptics. Cases of exacerbation of epilepsy by OCs have been reported (20, 24–26). OCs may also evoke phenytoin toxicity since steady-state plasma phenytoin concentrations in 40 oral contraceptive users were higher relative to phenytoin dose than in 135 age-matched non-users of OCs (27). The use of this combination has to be carefully assessed with respect to possible failure of contraception and increased incidence of fits. Paradoxically serum phenytoin concentrations may be raised to toxic levels. Whenever possible it would be better to advise alternative methods of contraception.

## 2. Interactions by which OCs Modify the Effects of Concomitant Medication

**Oral contraceptive/  
anticoagulant**

No patient who requires anticoagulants should use oral contraceptives since OCs increase the synthesis of specific blood coagulation factors (28) and may impair the efficacy of anticoagulant therapy.

The thromboembolic potential of OCs may impair the efficacy of anticoagulant therapy. This is of importance in anticoagulating women with deep vein thrombosis caused by taking OCs, since higher doses of anticoagulants may be required for some days even after stopping OCs.

Paradoxically, although the effects of dicoumarol were reduced by OCs (29), there have been reports of potentiation of the action of nicoumalone by OC use (15, 30). OCs have also increased the clearance of phenprocoumon without altering its anticoagulant effect (31).

There has been much published about the influence of OC therapy on thromboembolic disorders in women;

*Combination**Interaction*

this is relevant to the understanding of the importance of this interaction. A brief account of this influence is given below.

The Oxford Family Planning Association contraceptive study reported on 105 women suffering a first attack of venous thromboembolism unassociated with pregnancy or the puerperium (32).

In 71 women suffering thromboembolism unassociated with surgery, there was a strong association between current oral contraceptive use and certain or probable thromboembolism (relative risk 7.2). A weaker association with possible thromboembolism (relative risk 3.1) was found and little or no association with venous thromboembolism (relative risk 1.4).

There was no significant association between risk and duration of usage. In current users of OCs containing 50 µg or more of oestrogen, 20 cases of certain or probable thromboembolism occurred during 32 082 woman-years of observation, and in those using preparations of less than 50 µg of oestrogen three cases during 7606 woman-years. The corresponding figures for possible thromboembolism were nine and zero cases, respectively. Possible thromboembolism occurred in only one patient receiving a progestogen-only preparation.

Analysis of the data on the 34 cases of post-operative thromboembolism showed a difference between the incidence of thromboembolism in those using OCs during the month before surgery (12 out of 1244) and those who had not used OCs (22 out of 4359); although this difference was not significant. The findings of this study were consistent with the view that the risk of thromboembolism is lower with OCs containing less than 50 µg of oestrogen, although the data available were too few to confirm this. Further studies have been done to clarify this point (33–35), and they have suggested that the relative risk of developing thromboembolic disorders was increased in OC users even those taking low oestrogen preparations, although high oestrogen users were at a greater risk than those taking low oestrogen OCs. Women with the factor V Leiden mutation, a

<i>Combination</i>	<i>Interaction</i>
<b>Oral contraceptive/ anticoagulant cont.</b>	<p>hereditary abnormality which results in resistance to the anticoagulant effect of protein C, were at greater risk of developing venous thrombosis when taking OCs than were control subjects (35). The Committee on Safety of Medicines in the UK has recently announced that there was evidence of an increased risk of venous thromboembolism with combined OC preparations containing desogestrel or gestodene compared with those containing other progestogens (2). This warning was based on publications to which the CSM had pre-publication access and were subsequently confirmed by other findings (3–7).</p>
<b>Oral contraceptive/ antidiabetic agent</b>	<p>The potential effect of OCs on glucose tolerance are of particular concern because of the risk that impaired glucose tolerance will exacerbate their cardiovascular effects (36). Early studies suggested that the prevalence of abnormal glucose tolerance in OC users was increased from about 4 to 35%, but subsequent studies produced conflicting results possibly due to failure to discriminate between types and doses of oestrogen and progestogen used. In one study 81% of diabetic patients required no change in insulin dosage when taking OCs, 17% required an increase of 8–20 units, and 2% required 20–40 units more per day (37).</p> <p>The decrease in glucose tolerance is related to both the oestrogen and the progestogen content of the OC preparation. Levonorgestrel is the most potent progestogen in decreasing glucose tolerance (38), whereas OCs containing norethisterone are thought not to decrease glucose tolerance (39). However, a subsequent study suggested that glucose tolerance testing may not be the best way of assessing the effects of OCs on carbohydrate metabolism (40). This study which also measured insulin and C-peptide production found that, although levonorgestrel-containing combined OCs had a greater effect on glucose tolerance, desogestrel- or norethindrone-containing preparations produced a similar degree of insulin resistance, suggesting that this depends on the</p>

<i>Combination</i>	<i>Interaction</i>
	<p>oestrogenic component, and is modified by the progestogen. Despite these effects, oral contraceptives do not appear to increase the subsequent risk of developing type 2 diabetes (41). The use of other methods of contraception may be required for type 1 diabetic patients. If this is not practical, the patient should be checked more closely for decreased diabetic control, and modification of existing insulin therapy may be required. The risk of cardiovascular complications and microangiopathic changes may be increased when OCs are used (37).</p>
<b>Oral contraceptive/ antihypertensive</b> Cyclopenthiazide Guanethidine Methyldopa	<p>There is good evidence that women taking combined oral contraceptives develop higher systolic (3.6–5.0 mmHg) and diastolic (1.9–2.7 mmHg) blood pressure than control subjects using intrauterine contraceptive devices (42–44). It may therefore be inferred that oral contraceptives could reduce the effects of antihypertensive medication. This has been demonstrated with the earlier antihypertensives and reduced efficacy of cyclopenthiazide, guanethidine and methyldopa has been reported in patients taking OCs. This is probably due to contraceptive-induced Na<sup>+</sup> and water retention (20, 45). Oestrogens and combined oral contraceptives will antagonize the hypotensive actions of ACE inhibitors, β-blockers and diuretics (19).</p> <p>Plasma metoprolol concentrations were increased in some women taking oral contraceptives (46). Oral contraceptives may have to be stopped to treat hypertension adequately.</p>
<b>Oral contraceptive/ corticosteroid (20)</b>	<p>Oestrogens enhance the anti-inflammatory action of corticosteroids (47) and also retard the metabolism of cortisol (hydrocortisone) possibly by its increased binding to globulin (47). Contraceptive failure has been reported in women using intrauterine devices and using corticosteroid therapy (48). There have been several reports of enhanced effects of corticosteroids in women receiving oestrogens or OCs; the dose of corticosteroid may have to be reduced (16, 48).</p>

<i>Combination</i>	<i>Interaction</i>
<b>Oral contraceptive/folic acid and vitamin B<sub>12</sub></b>	<p>Oral contraceptives impair folate metabolism and produce some degree of folate depletion, although the mechanism of this is unclear (49). Serum and erythrocyte levels of folate are decreased and the urinary excretion of formiminoglutamic acid (an intermediary product of histidine metabolism that requires the reduced form of folic acid to be further metabolized) increases in women using OCs, although these levels return to normal within 3 months of stopping OCs.</p> <p>Oral contraceptives have also been shown to lower the serum levels of vitamin B<sub>12</sub>, although there is no evidence of tissue depletion. This is probably due to lower total vitamin B<sub>12</sub> serum binding capacity, rather than a true deficiency of the vitamin. However, pernicious anaemia may occur in women of reproductive age and a low vitamin B<sub>12</sub> level in woman taking OCs should not be disregarded until the possibility of malabsorption has been excluded. Folic acid therapy (10 mg daily for 3 months) has improved cervical dysplasia in users of OCs (50).</p> <p>Since pregnant women are predisposed to the development of folate deficiency, women who become pregnant shortly after discontinuing the use of OCs may be at a higher risk and adequate folate supplements should be taken. In view of the association between folate deficiency and fetal abnormality (particularly spina bifida), it would be prudent to advise all women coming off the pill and wishing to become pregnant to take folate supplements (51–53).</p>
<b>Oral contraceptive/pethidine (meperidine)</b>	Possible increased analgesia and CNS depression due to inhibition of pethidine's metabolism. This combination should be used with extreme care (54, 55).
<b>Oral contraceptive/phenothiazines</b>	Combined oral contraceptives may potentiate phenothiazine-stimulated prolactin secretion resulting in mammary hypertrophy and galactorrhoea. Other drugs which are prolactin-secretion stimulators (e.g.

<i>Combination</i>	<i>Interaction</i>
<b>Oral contraceptive/ miscellaneous drugs</b> e.g. benzodiazepines, xanthines, analgesics alcohol	reserpine, methyldopa and imipramine) may cause similar potentiation (20, 56, 57).
	Compounds undergoing oxidative metabolism may have their plasma concentrations raised by the inhibitory action of OCs. Conversely, OCs appear to induce glucuronidation of some drugs thus reducing their plasma concentrations. Examples are some benzodiazepines (clearance of chlordiazepoxide, alprazolam, diazepam and nitrazepam is reduced, clearance of temazepam is increased), xanthines (clearance of theophylline and caffeine is reduced), cyclosporin (clearance is reduced), analgesics (clearance of salicylic acid, paracetamol and morphine is increased) and alcohol (clearance is reduced or not affected) (see reviews (14–17, 58, 59)).

### 3. Interactions which may Potentiate the Side Effects of Oral Contraceptives

<b>Oral contraceptive/drugs causing liver enzyme inhibition</b>	A wide range of drugs are reported (see below) to cause liver enzyme inhibition. Concomitant administration with OCs could, <i>theoretically</i> , be expected to potentiate the actions of OCs by delaying the hepatic metabolism of both the oestrogen and progestogen components. This effect could present as increased side effects (e.g. fluid retention, diabetogenic and hypertensive effects, or increased risk of thromboembolic disorders). Such combinations should be used with care and subjects should be questioned/monitored at regular intervals for emergence of known side effects of OCs. Drugs that could be involved are: aspirin, allopurinol, chloramphenicol, cimetidine, cortisol and other corticosteroids, disulfiram, isoniazid, methandienone, methylphenidate, MAOI antidepressants, <i>para</i> -aminosalicylic acid, phenothiazines, phenyramidol, selective serotonin re-uptake inhibitors (SSRIs), sulphaphenazole, tricyclic antidepressants and related compounds, triparanol (23, 60).
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# **CHAPTER 8**

**Drug Interactions with Agents Used  
in Immunosuppression and Cancer  
Chemotherapy**

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## **8.1 DRUG INTERACTIONS WITH IMMUNOSUPPRESSANTS**

Immunosuppressants are used to prolong the survival of organ transplants by suppression of rejection processes. The major immunosuppressants are cyclosporin, azathioprine and tacrolimus. These agents are also used as immunosuppressants in autoimmune disorders. In addition, the following antineoplastic agents that possess immunosuppressant properties are also used in a variety of autoimmune disorders including those conditions affecting the skin, kidneys and joints: actinomycin D, chlorambucil, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, fluorouracil, hydroxyurea, melphalan, mercaptopurine, methotrexate, mustine, razoxane and thioguanine. These agents may be given in association with corticosteroids, the other main group of immunosuppressants, to permit a reduction in the dose level of corticosteroids that would be required were they used alone. The neoplastic agents are also used in conditions refractory to corticosteroids and other therapy.

The following chapter is selective in that it only deals with interactions involving the three main immunosuppressants. Interactions with antineoplastic agents and corticosteroids are dealt with in other chapters.

### **I. AZATHIOPRINE**

Azathioprine is an immunosuppressant and antineoplastic agent with similar actions to those of mercaptopurine to which it is slowly metabolized. It is given by mouth or by slow intravenous injection (well diluted) as the sodium salt. Blood counts should be carried out regularly during treatment and azathioprine should be withdrawn or the dosage reduced at the first indication of bone marrow depression. It should be used with care in patients with liver damage or a history of liver disease. Reduced doses may be required in patients with impaired renal function. Its dosage and duration of use may vary according to the condition, its severity and the clinical response obtained. Cessation of therapy, even after a period of years, carries a high risk of transplant rejection within a few weeks. It should be used with caution in patients receiving, or who have recently received, other drugs which suppress bone marrow function.

In addition to its role as an antineoplastic agent and in the prevention of transplant rejection, azathioprine is used in the treatment of patients with ulcerative colitis at doses of 2 mg/kg/day that have not been controlled by salazopyrine type agents alone, e.g. mesalazine or olsalazine. Azathioprine is also used in severe rheumatoid arthritis at doses of 1.5–2.5 mg/kg/day in divided doses. In immunosuppressant therapy in systemic lupus erythematosus and polymyositis, when azathioprine is

used, it is usual to combine its use with chlorambucil. In the treatment of psoriatic arthritis there is the clinical belief that azathioprine is more effective for the arthritic element and methotrexate for the dermatological manifestations.

In myasthenia gravis where thymectomy is not advisable immunosuppression with corticosteroids (prednisolone 100 mg daily initially) may be given. Since high doses of steroids may be necessary the addition of azathioprine 2 mg/kg daily may have a major corticosteroid-sparing effect.

There is clinical evidence that azathioprine antagonizes the effect of non-depolarizing muscle-relaxants (e.g. atracurium, *d*-tubocurarine, pancuronium, vecuronium). Experimental data confirm that azathioprine reverses the neuromuscular block caused by *d*-tubocurarine, and it potentiates the neuromuscular blocking action of suxamethonium.

The potential teratogenicity of azathioprine should be borne in mind. Although it has been shown to be teratogenic in laboratory animals, clinical evidence suggests that the risk is not appreciable in humans. There is no doubt that azathioprine and its metabolites cross the placenta; many children exposed *in utero* have now completed the first decade of life without reported problems. It has not been possible to detect azathioprine or its metabolites in the breast milk of treated patients.

Tablets and injection solutions should be stored below 25°C and protected from light.

<i>Combination</i>	<i>Interaction</i>
<b>Alkaline solutions/ azathioprine (1)</b>	Azathioprine is metabolized to mercaptopurine at alkaline pH. Avoid admixture of azathioprine with any alkaline solution.
<b>Allopurinol, oxypurinol, thiopurinol/azathioprine (2, 3)</b>	Xanthine oxidase activity is inhibited by allopurinol, oxypurinol and thiopurinol which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid. The dose of azathioprine should be reduced to one quarter of the original dose if given in combination with a xanthine oxidase inhibitor.
<b>Co-trimoxazole/ azathioprine (4)</b>	Haematological toxicity (bone marrow suppression) of co-trimoxazole is increased by accompanying immunosuppression with azathioprine, especially when co-trimoxazole is used in prophylaxis rather than in treatment of infection.

<i>Combination</i>	<i>Interaction</i>
<b>Frusemide/azathioprine</b> (3)	Frusemide impairs the metabolism of azathioprine by human hepatic tissue <i>in vitro</i> . The significance of this clinically is uncertain.
<b>Neuromuscular blocking agents/azathioprine</b> (3, 5, 6)	Azathioprine potentiates the neuromuscular blockade produced by depolarizing agents such as succinylcholine and can reduce the blockade produced by non-depolarizing agents such as atracurium, vecuronium, pancuronium, and tubocurarine. There is considerable variation in the potency of this interaction.
<b>Myelo suppressive agents/ azathioprine</b> (3)	A number of therapeutic agents have myelosuppressive effects, e.g. antineoplastic agents, cimetidine, co-trimoxazole, indomethacin, penicillamine sulphonamides, etc. These effects are more common and more pronounced in patients concomitantly treated with azathioprine.
<b>Rifampicin/azathioprine</b> (7)	Rifampicin reduces the efficacy of azathioprine in rejection of transplanted organs.
<b>Sulphasalazine/ azathioprine</b> (8, 11)	Thiopurine drugs, such as azathioprine and 6-mercaptopurine, are used in the treatment of inflammatory bowel disease, as are sulphasalazine (salazopyrine) and its metabolite 5-amino salicylic acid. S-Methylation catalyzed by thiopurine methyl transferase (TPMT) is a major pathway in the metabolism of thiopurines. Non-competitive inhibition of thiopurine methyl transferase by sulphasalazine has been demonstrated. Individuals with genetically low levels of TPMT are at greatly increased risk of potentially life-threatening thiopurine toxicity such as myelosuppression when treated with standard doses of both drugs.
<b>Vaccines/azathioprine</b> (3)	The immunosuppressive activity of azathioprine could result in atypical and life-threatening infections in response to live vaccines. Killed vaccines are likely to be ineffective when given to patients on azathioprine. Hepatitis B vaccine being a case in point.

<i>Combination</i>	<i>Interaction</i>
<b>Warfarin/azathioprine</b> (3, 12)	Inhibition of the anticoagulant effect of warfarin in azathioprine-treated patients has been reported (3). Severe bleeding occurred in a patient on long-term warfarin treatment after discontinuing azathioprine.

## II. CYCLOSPORIN

Cyclosporin is a fungal metabolite, it is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent which prolongs the survival of allogenic transplants involving skin, heart, pancreas, bone marrow, kidney, lung, etc. It appears to block the resting lymphocytes in the G<sub>0</sub> or early G<sub>1</sub> phase of the cell cycle and also inhibits lymphokine production and release, including interleukin 2 (T-cell growth factor, TCGF). The available evidence suggests that cyclosporin acts specifically and reversibly on lymphocytes. It does not depress haemopoiesis and has no effect on the function of phagocytic cells.

Cyclosporin is extensively metabolized by the liver. Metabolism is thought to proceed via the cytochrome P450 system, primarily by mono- and dihydroxylation as well as by N-demethylation. The major route of elimination is biliary and most of the drug is excreted in the bile as metabolites. Only trace amounts of cyclosporin and its metabolites are eliminated in the urine.

Interactions with other drugs generally arise from effects on the pharmacokinetics of cyclosporin (increased or decreased cyclosporin blood levels), or from additive pharmacological or toxicological effects resulting in nephrotoxicity and/or hepatotoxicity (see reviews by Cockburn (13), Ptachcinski *et al.* (14) and Whiting *et al.* (15)).

Listed below in the Drug Interaction Tables are those drugs which have been reported to interact in some way with cyclosporin. The commonest hazards of such interactions are raised cyclosporin blood levels (danger of nephrotoxicity and hepatotoxicity) and decreased cyclosporin blood levels (danger of transplant rejection). Management of these interactions (assuming that the interacting drug must be continued) will depend on adjusting cyclosporin dosage with specific monitoring of renal function. The list of interactions is divided into those which are well substantiated by clinical reports, those which are based on isolated reports which have yet to be substantiated or refuted, and those which have the potential to cause an interaction, but for which no published cases have arisen. Relevant results from animal studies have also been cited.

The extent of a given interaction and its clinical significance will be variable and may depend upon numerous other factors such as the patient's condition, drug dosage and mode of administration. In most cases, because of the nature of the combined drugs, concomitant administration *would not be contraindicated* and indeed may be unavoidable. Consideration should therefore be given to the poten-

tial for interaction in such cases. Routine monitoring of cyclosporin blood levels should always be conducted and dosage adjustments instituted whenever necessary.

Animal studies indicate that cyclosporin is not teratogenic. However, as the safety of cyclosporin in human pregnancy has not been fully established it should, therefore, only be used if the benefit outweighs any potential risk. Cyclosporin passes into breast milk and the manufacturers recommend that mothers receiving treatment with cyclosporin should not breast feed their infants.

Cyclosporin (Sandimmune) is presented as an oral solution (100 mg/ml) and as a concentrate for intravenous infusion. The latter concentrate (50 mg/ml) contains 650 mg/ml polyethoxylated castor oil and 33% ethanol by volume. This formulation should therefore not be used in patients known to be hypersensitive to polyethoxylated castor oils (Cremophor EL). The alcohol content of the formulation may also be anticipated to present a hazard to patients being treated with disulfiram (Antabuse) or other drugs which have an antabuse-like reaction with alcohol.

Once an ampoule of the concentrated formulation is opened the contents should be used immediately; diluted infusion solutions should be discarded after 24 hr. The oral solution should be used within 2 months of opening the bottle. Refrigeration of the oral solution is not recommended as this may result in precipitation of cyclosporin.

## 1. Drugs Increasing Serum Cyclosporin Levels (*danger of nephrotoxicity*)

### a. Well-substantiated interactions

#### **Corticosteroids** (16)

e.g. methyl prednisolone (17–21)

prednisolone (21)

prednisone (22–24)

#### **Calcium channel blocker**

e.g. diltiazem (16, 25–28)

nicardapine (16, 52)

verapamil (16, 61, 62)

#### **doxycycline** (13–16)

**erythromycin** (16, 29–39)

#### **fluconazole** (16)

#### **itraconazole** (16)

**ketoconazole** (16, 40–49)

**norethisterone** (50–51)

**omeprazole** (7)

#### **Oral contraceptives** (51)

### b. Isolated reports of interactions

**acyclovir** (15, 53)

**amiodarone** (7)

**ceftazidime** (54, 55)  
**cimetidine** (56–60)  
**clotrimazole** (14)  
**co-trimoxazole** (67–69)  
**danazol** (50, 69)  
**diltiazem** (63)  
**frusemide** (77, 78)  
**guanfacine** (70)  
**imipenem** (72)  
**latamoxef sodium** (73)  
**methyl testosterone** (74)  
**norfloxacin** (64)  
**propafenone** (7)  
**ranitidine** (75–76)  
**thiazide diuretics** (13, 15)  
**warfarin** (13)

## **2. Drugs Decreasing Serum Cyclosporin Levels (*danger of transplant rejection*)**

**carbamazepine** (16, 79)  
**isoniazid** (24, 80–82)  
**phenobarbitone** (16, 83–88)  
**phenytoin** (16, 57, 89–92)  
**primidone** (13, 73)  
**rifampicin** (16, 80–82, 93–100)  
**sodium valproate** (101)  
**sulphonamide/trimethoprim combinations** (102, 103)  
**sulphinpyrazone** (104)

## **3. Drugs Enhancing Cyclosporin's Nephrotoxic Potential**

**acetazolamide** (65)  
**acyclovir** (51)  
**aminoglycosides** (105–110)  
**amphotericin** (111–113)  
**captopril** (13, 114)  
**cephalosporins** (106, 107)  
e.g. **cefotaxime** (56)  
**cefuroxime** (56)  
**cephradine** (56)  
**cimetidine** (57–59)  
**colchicine** (7)  
**etoposide** (115)  
**frusemide** (77, 78, 116)  
**indomethacin** (14, 117)

- melphalan** (44, 118–120)
- metolazone** (121)
- non-steroidal anti-inflammatory drugs (NSAIDs)** (14, 66, 117, 122)
- ranitidine** (58, 76, 123)
- sulphonamides/co-trimoxazole** (67, 68, 124)
- trimethoprim** (67, 102, 124)
- vancomycin** (125)

#### 4. Other Interactions with Cyclosporin

<i>Combination</i>	<i>Interaction</i>
<b>Digoxin/cyclosporin</b> (13)	Increased levels of plasma digoxin in patients receiving combination.
<b>Diuretics/cyclosporin</b> (15)	Possible hyperkalaemia with potassium sparing diuretics or with K <sup>+</sup> supplement.
<b>Fluoxetine/cyclosporin</b> (126)	Horton and Bonser (126) reported an interaction between cyclosporin and fluoxetine causing a rise in blood cyclosporin concentrations. Their patient, a 59-year-old man, underwent cardiac transplantation for end stage heart failure. Cyclosporin was given as an immunosuppressant, and he was maintained on 225 mg twice daily with a stable trough whole blood concentration of 300 µg/l. Seventeen days post-operatively, the patient developed an acute depressive illness and was given the serotonin re-uptake inhibitor antidepressant, fluoxetine 20 mg once daily. No other changes were made to his drug treatment.  After 10 days his cyclosporin concentration had risen to 588 µg/l and the dose of cyclosporin was reduced to 75 mg twice daily. Cyclosporin blood concentration then remained at 250 µg/l. He did not respond to fluoxetine, so the drug was stopped. After 7 days his cyclosporin concentration had fallen to 95 µg/l, necessitating a dose increase of cyclosporin to 200 mg twice daily. His blood cyclosporin concentration then remained at 300 µg/l. Hepatic and renal functions were normal throughout.
<b>Grapefruit juice/cyclosporin</b> (127–130)	The flavonoids in grapefruit juice inhibit the breakdown of cyclosporin and increase the steady state blood levels.

<i>Combination</i>	<i>Interaction</i>
<b>Lipid lowering agents/cyclosporin (7)</b>	Increased risk of myopathy with pravastatin and simvastatin.
<b>Nifedipine/cyclosporin (131, 132)</b>	Psoriatic patients receiving nifedipine together with cyclosporin showed evidence of nifedipine toxicity (severe flushing, burning sensation, rash) (131). Cyclosporin was shown to compete with nifedipine for a common metabolic enzyme (132) cytochrome P450 which reduced the metabolism of nifedipine.
<b>Neuromuscular blocking agents/cyclosporin e.g. atracurium and vecuronium (133)</b>	Increased neuromuscular blockade.
<b>Prednisolone/cyclosporin (21, 134–140)</b>	Increased prednisolone levels due to decreased hepatic metabolizing activity (cyclosporin inhibits liver enzymes). There is a mutual interaction in that cyclosporin blood levels are also increased.  Small doses of corticosteroids are used with advantage in cyclosporin treatment; however, Cushingoid symptoms have commonly been reported, as has also impaired glucose metabolism in pancreas graft recipients. Prednisolone dosage should be kept at the minimal effective level.
<b>Vaccines/cyclosporin (141–146)</b>	With killed vaccines there is reduced efficacy of the vaccine due to immunosuppression. With live vaccines there is a significant risk of severe infection.  Prospective cyclosporin therapy warrants assessment of each patient's immune protection against infectious diseases preventable with vaccines or toxoids.

## TACROLIMUS

Tacrolimus is isolated from *Streptomyces tsukubaensis* and has a 23-member macro-lide lactone structure with a hemiketal-masked  $\alpha$ - $\beta$  diketoamide function. It is used as an immunosuppressant in transplantation and in various immunological diseases.

Tacrolimus has a low and variable bioavailability and is mainly excreted in the

bile following metabolism. The drug has a low therapeutic index and its use is mainly limited by its intrinsic nephrotoxicity and neurotoxicity.

The Committee on Safety of Medicines (147) drew attention to Atkinson *et al.* (148) who reported five cases of cardiomyopathy in children who received tacrolimus after liver or kidney transplantation. The CSM point out that in those cases where blood levels are known the recommended level of tacrolimus of 25 µg/ml had been exceeded.

Cardiomyopathy associated with tacrolimus appears to be reversible on dose reduction or drug withdrawal.

In the liver and small intestine, tacrolimus is mainly metabolized by enzymes of the cytochrome P450 (CYP)3A sub family to at least eight demethylated and/or hydroxylated metabolites.

Anecdotal *in vivo* drug interactions involving known CYP3A substrates/or inhibitors in patients who have received liver transplantation have been reported (150) which have given rise to increased plasma levels of tacrolimus. In a comprehensive study (149) using 34 different drugs Christians *et al.* (1996) studied their potential for interaction with tacrolimus metabolism using human liver microsomes.

#### **Drugs Which Have Been Shown to Inhibit Tacrolimus Metabolism**

<i>In vivo</i> (150)	<i>In vitro</i> (149)
clotrimazole (151)	bromocriptine
corticosteroids	corticosteroids
ketoconazole	dexamethasone
diltiazem	ergotamine
erythromycin (152, 153)	ethinyloestradiol
	josamycin
	ketoconazole
	miconazole
	midazolam
	nifedipine
	omeprazole
	tamoxifen
	troleandomycin
	verapamil

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## **8.2. DRUG INTERACTIONS WITH ANTINEOPLASTIC AGENTS**

The chemical structures of these agents is very diverse but some form of classification has been made on the basis of their mode of action or origin. Almost all these agents are teratogenic or fetotoxic, and almost all the agents cause a greater or lesser degree of bone marrow suppression, they may also be immunosuppressant leaving the patient's resistance to disease, particularly viral infections, impaired.

Most agents have to be administered intravenously and this may give rise to drug/drug or drug suspension incompatibilities. These have not been dealt with since there are adequate instructions in the package inserts to enable the doctor or pharmacist to deal with this problem adequately.

These drugs are in general only suitable for hospital use by specialists in chemotherapy. Special precautions should be observed when handling cytotoxic agents, these principles are given below.

- (1) trained personnel should reconstitute cytotoxics;
- (2) reconstitution should be carried out in designated areas;
- (3) protective clothing (including gloves) should be worn;
- (4) the eyes should be protected and means of first aid should be specified;
- (5) pregnant staff should not handle cytotoxics;
- (6) adequate care should be taken in the disposal of waste material, including syringes, containers and absorbent material.

Virtually all cytotoxic agents are locally toxic and seepage from the infusion site can result in severe tissue necrosis.

### **GROUP I: ALKYLATING AGENTS**

This group of cytotoxic drugs are probably the most widely used in cancer chemotherapy. They act by damaging DNA thus interfering with cell replication. As a result gametogenesis is often severely affected, also when combined with extensive radiation is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

Regimens that contain an alkylating drug carry the risk of causing permanent male sterility (there is no effect on potency). Sperm storage before commencing treatment may be advisable. Females are less severely affected although reproductive life may be shortened by the onset of an early menopause. No increase in fetal

abnormalities or abortion rate has been recorded in patients who remain fertile after treatment.

**Busulphan**

**Carmustine:** can induce progressive pulmonary fibrosis particularly in children (6)

**Chlorambucil****Cyclophosphamide****Estramustine****Ethoglucid****Hexamethyl melamine**

**Ifosfamide:** can cause pulmonary fibrosis

**Lomustine****Melphalan****Mitobronitol****Mustine hydrochloride****Pipobroman****Thiotepa****Theosulfan****Uramustine**

*Urothelial toxicity*, manifest by haemorrhagic cystitis is a peculiar problem associated with the use of cyclophosphamide or ifosfamide, is caused by their acrolein metabolite. *Mesna* reacts specifically with this metabolite in the urinary tract preventing this aspect of these drugs toxicity.

**GROUP II: CYTOTOXIC ANTIBIOTICS**

Many of this diverse group of drugs act as radiomimetics and simultaneous use of radiotherapy should be avoided as the effects of radiotherapy can be markedly enhanced.

**Aclarubicin**

**Bleomycin:** the principal problem associated with bleomycin use is progressive pulmonary-fibrosis.

**Dactinomycin (actinomycin D)****Daunorubicin**

**Doxorubicin (adriamycin):** common toxic effects are nausea, vomiting, myelosuppression, alopecia. Supraventricular tachycardia may be associated with its usage, in high doses there may be cumulation and this is associated with the development of cardiomyopathy, which may manifest itself 1–6 months from initiation of therapy. Severe cardiac failure can occur without warning.

**Epirubicin:** blood counts and cardiac function should be carefully monitored during epirubicin treatment.

**Idarubicin**

**Mitomycin**

**Mitozantrone:** mitozantrone can cause congestive heart failure and decreases in left ventricular ejection fraction.

**Plicamycin:** the most important form of toxicity associated with the use of plicamycin consists of a bleeding syndrome which usually begins with an epistaxis. There may be one or several episodes which usually progress no further. More rarely it may present with haematemesis. Plicamycin can induce multiple abnormalities in clotting factors.

**GROUP III: VINCA ALKALOIDS**

All have similar activity causing metaphase arrest. All have similar therapeutic activity but vary in their predominant toxicity. The vinca alkaloids are used to treat acute leukaemias, lymphomas, and some solid tumours, e.g. breast and lung. The predominant toxic effect is peripheral and autonomic neuropathy. This side effect is most obvious with vincristine. The neuropathy is manifest by loss of tendon reflexes, paraesthesia, abdominal bloating and constipation. Significant motor weakness is a contraindication for the continued use of this class of drug. The incidence of neuropathy is also dependent on the tumour type being treated (1, 2).

**Vincristine sulphate** causes virtually no myelosuppression. Its use may be associated with alopecia and hyponatraemia as a result of stimulating inappropriate ADH secretion.

**Vinblastine sulphate** is more myelosuppressive than vincristine but causes less neurotoxicity.

**Vindesine sulphate**

*All three vinca alkaloids are administered intravenously.*

**GROUP IV: ANTIMETABOLITES**

Antimetabolites are incorporated into new nuclear material or combine irreversibly with cellular enzymes and prevent cell division.

**Azathioprine** (see also section on immunosuppressive agents).

**Cladribine**

**Cytarabine:** a 'cytarabine syndrome' has been described. It is characterized by fever, myalgia, bone pain, chest pain, maculopapular rash, conjunctivitis, and malaise occurring 6–12 hr after administration. Corticosteroid treatment may be necessary.

**Fludarabine phosphate:** when used in high doses in acute leukaemia, fludarabine was associated with severe neurological effects including blindness and death. Rare cases of haemolytic anaemia have also been reported.

**Fluorouracil****Gemcitabine**

**Mercaptopurine****Methotrexate****Thioguanine****GROUP V: OTHER ANTINEOPLASTIC AGENTS**

**Amsacrine:** fatal arrhythmias have been reported associated with drug-induced hypokalaemia. The dose-limiting toxicity, however, is myelosuppression. A few cases of grand mal seizures in patients treated with amsacrine for acute leukaemia have been reported.

**Carboplatin** and **cisplatin:** cisplatin also has an alkylating action. Carboplatin has similar actions to cisplatin but is better tolerated. The incidence and severity of nausea, vomiting, nephrotoxicity, neurotoxicity and ototoxicity are all less with carboplatin than cisplatin. Carboplatin is, however, more myelosuppressive.

**Crisantaspase** is the enzyme asparaginase prepared from *Erwina chrysanthemi*.

**Darcarbazine****Ethoglucid****Etoposide****Hydroxyurea****Interleukin 2**

**Paclitaxel** is the first of a new class of drug, the taxanes, and is prepared from the Pacific yew. It is the first of a class of agents that promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization. This stability results in inhibition of the reorganization of the microtubule network essential for interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple esters of microtubules during mitosis. Routine premedication with a corticosteroid, an antihistamine, an H<sub>2</sub> receptor blocker is recommended to prevent severe hypersensitivity reactions. Other side effects include bone marrow suppression, peripheral neuropathy, cardiac conduction abnormalities and alopecia. Arthralgia and myalgia are reported to affect 54% of patients and in 12% are severe (3).

*Paclitaxel is formulated with polyethoxylated castor oil which is associated with anaphylaxis (3).*

**Pentostatin****Procarbazine****Razoxane****Tamoxifen****COMBINATION CHEMOTHERAPY**

Cytostatic or antineoplastic agents are frequently given in treatment schedules which involve therapy with multiple drugs. This judicious use of triple and quadruple drug

therapy in these regimens is probably the major advance in treatment of malignant disease, particularly in leukoproliferative diseases, in recent years rather than the introduction of any new single agent. Interactions between different cytostatic or antineoplastic drugs in multiple therapy will not be discussed in this section, but a list of the more common multiple regimens is given.

*The following regimens, for example, have been used to treat acute leukaemias:*

- CAMP: cyclophosphamide + methotrexate + mercaptourine + prednisolone
- CART: cytarabine + colaspase + daunorubicin + thioguanine
- COAP: cyclophosphamide + OAP
- DOAP: daunorubicin + OAP
- L2: prednisolone + vincristine + daunorubicin for induction, cytarabine + thioguanine + colaspase + carmustine for consolidation, and thioguanine + cyclophosphamide + hydroxyurea + daunorubicin + methotrexate + carmustine + cytarabine + vincristine for maintenance
- OAP: vincristine + cytarabine + prednisone
- VAMP: vincristine + methotrexate + mercaptourine + prednisolone.

*The following regimens, for example, are used for Hodgkin's disease and lymphoma:*

- COPP: cyclophosphamide + vincristine + procarbazine + prednisone
- MOPP: mustine + vincristine + procarbazine + prednisone
- ABVD: doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine.

Regimens using multiple cytostatic or antineoplastic agents are a highly specialized therapeutic exercise and their use should be left to experts. The object of the following table is therefore to draw attention to the fact that other drugs may interact with these antineoplastic agents.

## I. INTERACTIONS WITH ALKYLATING AGENTS

<i>Combination</i>	<i>Interaction</i>
<b>Busulphan/other drugs causing gynaecomastia (4)</b> e.g. digitalis glycosides ethionamide griseofulvin phenothiazines spironolactone	Busulphan causes gynaecomastia; this effect may be potentiated or additive when this agent is given to patients receiving other drugs known to cause gynaecomastia (4).

<i>Combination</i>	<i>Interaction</i>
<b>Busulphan/thioguanine (5)</b>	The combination of busulphan with thioguanine has resulted in the development of nodular regenerative hyperplasia in the liver, portal hypertension and oesophageal varices (5).
<b>Chlorambucil/phenylbutazone (7)</b>	Animal studies have indicated that patients who receive phenylbutazone may require a reduction in the standard dose of chlorambucil because of the possibility of enhanced chlorambucil toxicity.
<b>Cyclophosphamide/allopurinol (8, 9, 10)</b>	The Boston Collaborative Drug Surveillance Program (10) found that in patients with neoplastic disease, other than leukemia, bone marrow suppression occurred in 18.8% of cases treated with cyclophosphamide alone, but in 58.8% of cases treated with cyclophosphamide plus allopurinol. Allopurinol potentiates the toxic effects of cyclophosphamide on bone marrow.
<b>Cyclophosphamide/antidiabetic agent (11, 12)</b>	Cyclophosphamide has been reported to be diabetogenic (11), and in other reports to depress blood sugar concentrations (12). It would therefore be expected to upset the stability of a patient controlled on insulin or oral hypoglycaemic drugs.
<b>Cyclophosphamide/skeletal muscle relaxant (13)</b>	Cyclophosphamide lowers the serum pseudocholinesterase level and may give rise to prolonged apnoea if suxamethonium or other depolarizing neuromuscular blocking drug is given. Check serum pseudocholinesterase level before anaesthesia. Avoid suxamethonium in such cases.
<b>Ifosfamide/warfarin (14)</b>	Ifosfamide potentiates the effect of warfarin.
<b>Lomustine/theophylline (9)</b>	The combination of theophylline and lomustine accelerated the leucopenia and thrombocytopenia common with this alkylating agent. Theophylline-induced phosphodiesterase inhibition in platelets increases intracellular cyclic AMP levels and may inhibit platelet function. Oncologists should be alert to the possibility of

<i>Combination</i>	<i>Interaction</i>
	augmented myelotoxicity and thrombopathia with this combination.
<b>Melphalan/nalidixic acid (15)</b>	Nalidixic acid together with high dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis.
<b>Thiotepa/skeletal muscle relaxant (13)</b>	<p>Thiotepa lowers the serum pseudocholinesterase level and may give rise to prolonged apnoea if suxamethonium or other depolarizing neuromuscular blocking drug is given.</p> <p>Check levels of pseudocholinesterase in patients on thiotepa treatment; if levels are low avoid the use of suxamethonium or other depolarizing neuromuscular blocking drug. If suxamethonium is necessary in such cases the anaesthetist should be aware of the risk of prolonged apnoea.</p>

## II. INTERACTIONS WITH CYTOTOXIC ANTIBIOTICS

<b>Bleomycin/divalent and trivalent cations and various drugs in solution (16, 17)</b>	Bleomycin chelates divalent and trivalent cations (especially copper) and may be precipitated from solution. Bleomycin is also incompatible with amino acids, aminophylline, ascorbic acid, dexamethasone, frusemide (furosemide), riboflavin and agents containing sulphhydryl groups.
<b>Bleomycin/nephrotoxic agents e.g. cisplatin (18–20)</b>	Enhanced pulmonary toxicity has been reported in some patients given bleomycin and cisplatin. This has been attributed to cisplatin-induced impairment of renal function leading to a decrease in bleomycin elimination. It seems reasonable to assume that similar interactions might occur if bleomycin were given with other nephrotoxic agents.
<b>Dactinomycin/cellulose filters (21–23)</b>	Drug binds to cellulose ester membranes used in some in-line filters. Avoid the use of cellulose filters.

<i>Combination</i>	<i>Interaction</i>
<b>Dactinomycin/vaccination (22, 24)</b>	Vaccination for smallpox or use of other live vaccines or infection with chickenpox can lead to severe generalized disease which is sometimes fatal (24).  Administration of dactinomycin at or about the time of infection with chickenpox or herpes zoster can cause severe generalized disease which can be fatal (22).
<b>Daunorubicin/heparin sodium (25)</b>	Daunorubicin has been reported to be incompatible with heparin sodium in solution.
<b>Doxorubicin/aluminium-containing apparatus (26)</b>	Evidence suggests that there is a chemical reaction (precipitation or colour change) between doxorubicin hydrochloride injection solutions and the aluminium hub of a syringe needle.
<b>Doxorubicin/heparin sodium and other drugs in solution (27)</b>	Doxorubicin has been reported to be incompatible with solutions of heparin sodium, aminophylline, cephalothin sodium, dexamethasone, fluorouracil and hydrocortisone. Store solutions of doxorubicin in airtight containers at a temperature not exceeding 40°C; protect from light.
<b>Mithramycin/divalent cations e.g. Fe<sup>2+</sup> (28)</b>	Mithramycin readily chelates with divalent cations (especially Fe <sup>2+</sup> ). Avoid this contact especially with solutions containing trace elements.

### III. INTERACTIONS WITH VINCA ALKALOIDS

<i>Combination</i>	<i>Interaction</i>
<b>Vinca alkaloids/ anticonvulsants (29)</b>	Use of combination of anticancer chemotherapy including vinca alkaloids have been reported to reduce the blood levels of phenytoin and to increase risk of seizure.
<b>Vinca alkaloids/ L-asparaginase (29)</b>	When a vinca alkaloid is given with L-asparaginase it should be given 12–24 hr before the administration of L-asparaginase in order to minimize toxicity, since

<i>Combination</i>	<i>Interaction</i>
<b>Vinca alkaloids/ mitomycin-C (29)</b>	L-asparaginase reduces the hepatic clearance of vincristine.
	Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloids were used in combination with mitomycin C and may be serious when there is pre-existing pulmonary dysfunction. The onset may be within minutes, or several hours after the vinca alkaloid is injected, and may occur up to 2 weeks following a dose of mitomycin C. Progressive dyspnoea may occur. <i>Vinca alkaloids should not be re-administered.</i>

#### IV. INTERACTIONS WITH ANTIMETABOLITES

<i>Combination</i>	<i>Interaction</i>
<b>Azathioprine/alkaline solutions (30)</b>	Azathioprine is metabolized to mercaptopurine at alkaline pH. Avoid a mixture of azathioprine with any alkaline solution.
<b>Azathioprine/allopurinol (9)</b>	Azathioprine is converted to inactive metabolites by xanthine oxidase, and this enzyme is inhibited by allopurinol. The dose of azathioprine should be reduced if the two drugs are given together.
<b>Cytarabine/fluorouracil or methotrexate (31, 32, 33)</b>	Cytarabine is incompatible with solutions of fluorouracil or methotrexate. There is evidence that the latter two agents are also incompatible with each other in solution. Tumour studies in animals have shown that methotrexate and cytarabine inhibit the activity of each other <i>in vivo</i> (33).
<b>Fludarabine/dipyridamole (34)</b>	The efficiency of fludarabine is reduced by dipyridamole.
<b>Fludarabine/pentostatin (34)</b>	In a clinical investigation with pentostatin (deoxycoformycin) for the treatment of refractory

<i>Combination</i>	<i>Interaction</i>
<b>Fludarabine/pentostatin cont.</b>	chronic lymphatic leukaemia there was an unacceptably high incidence of fatal pulmonary toxicity. The combination is not recommended.
<b>Fluorouracil/allopurinol (35)</b>	Concurrent dosage with allopurinol and fluorouracil in 23 patients with advanced cancer enabled i.v. doses of 2 g/m <sup>2</sup> /day of fluorouracil to be tolerated. The combination permitted a fourfold increase in steady-state fluorouracil serum levels and in the 'concentration × time' exposure to fluorouracil. Protection by allopurinol was also seen in both gastrointestinal epithelium and marrow. Allopurinol is metabolized to oxypurinol which in turn is phosphorylated to 1-oxypurinol-5'-monophosphate, a potent inhibitor of orotidylate decarboxylase, inhibition of which leads to an accumulation of orotic acid, which in turn inhibits the intracellular conversion of fluorouracil to either fluorodeoxyuridine monophosphate or fluorouridine triphosphate, thereby reducing the toxicity of fluorouracil. This is an interaction that can be exploited to the benefit of the patient.
<b>Fluorouracil/cimetidine (36, 37)</b>	Pretreatment with cimetidine (1000 mg daily for 4 weeks) increased the bioavailability of oral fluorouracil by over 70% and of i.v. fluorouracil by 27%, without evidence of increased toxicity. In contrast to the previous study (79) cimetidine did not enhance the absorption of fluorouracil. No increase in toxicity was noted.
<b>Fluorouracil/other drugs in solution (31, 38)</b>	Fluorouracil is incompatible with the following drugs in solution; cytarabine, diazepam, doxorubicin and methotrexate. Solutions of fluorouracil are alkaline and therefore should not be mixed with acidic agents; e.g. amino-acids, insulin, multivitamins, penicillin or tetracyclines.
<b>Mercaptopurine/ allopurinol (9, 39, 40)</b>	Mercaptopurine is converted to inactive metabolites by xanthine oxidase; this enzyme is inhibited by allopurinol. The dose of mercaptopurine should be reduced by 75% if the two drugs are taken together.

<i>Combination</i>	<i>Interaction</i>
<b>Mercaptopurine/ anticoagulant</b> e.g. warfarin (39)	The anticoagulant effect of warfarin is reduced when mercaptopurine is co-administered.
<b>Mercaptopurine/ doxorubicin</b> (41)	Doxorubicin enhances the hepatotoxicity of mercaptopurine.
<b>Methotrexate/acidic drugs</b> aspirin (42–44) chloramphenicol (42) phenytoin (42) probencid (42, 45) propionic acid NSAIDS (42) sulphinpyrazone (42) sulphonamide (42, 46, 47) tetracyclines (42) thiazide diuretics (42)	Methotrexate is extensively protein bound and may displace or be displaced by other acid drugs. The concurrent administration of such drugs will also decrease the methotrexate transport function of renal tubules, thereby reducing excretion and increasing toxicity of methotrexate.
<b>Methotrexate/amiodarone</b> (54)	Ulcerated skin lesions developed in a patient maintained on methotrexate for psoriasis after the introduction of amiodarone.
<b>Methotrexate/smallpox vaccination</b> (48)	After primary vaccination, severe reaction with fever and vaccinia pustules has been described in patients treated with methotrexate for psoriasis. Do not vaccinate patients receiving methotrexate with 'live' virus vaccines.
<b>Methotrexate/smallpox vaccination plus corticosteroids</b> (49)	This combination can be fatal. Smallpox vaccination is contraindicated. All live vaccines should be avoided in such patients.
<b>Methotrexate/D-xylose</b> (46)	Methotrexate has been demonstrated to cause malabsorption of D-xylose in children with lymphoblastic leukaemia. The effect is less marked if the dosage of methotrexate is spaced more widely.

<i>Combination</i>	<i>Interaction</i>
<b>Methotrexate/other drugs in solution (32)</b>	Methotrexate is incompatible with the following drugs in solution: cytarabine, fluorouracil and prednisolone sodium phosphate.
<b>Thioguanine/busulphan (51)</b>	The combination of busulphan and thioguanine has resulted in the development of nodular regenerative hyperplasia, portal hypertension and oesophageal varices.
<b>Vidarabine/allopurinol (52)</b>	Severe neurotoxicity resulted from giving vidarabine treatment to two patients with chronic lymphocytic leukaemia who suffered herpes simplex or varicella zoster infections and who were receiving 300 mg allopurinol daily. The interaction was thought to be due to allopurinol causing an increase in the vidarabine metabolite, hypoxanthine arabinoside.

## V. INTERACTIONS WITH OTHER ANTINEOPLASTIC AGENTS

<i>Combination</i>	<i>Interaction</i>
<b>Cisplatin/aminoglycoside antibiotic (1)</b>	There is an increased risk of both nephrotoxicity and ototoxicity when cisplatin is used concomitantly with an aminoglycoside antibiotic.
<b>Cisplatin/antihypertensive and diuretic therapy (53)</b>	Severe nephrotoxicity was reported in a patient given cisplatin and antihypertensive therapy of frusemide, hydralazine, diazoxide and propranolol. On two subsequent occasions the same dose of cisplatin given alone had no effect on renal function. Results in animals have shown that frusemide aggravates cisplatin nephrotoxicity.
<b>Cisplatin/lithium 55, 56)</b>	Cisplatin is reported to alter the proximal tubular reabsorption of calcium and magnesium. Lithium, being also reabsorbed in the proximal tubule, is a likely candidate for drug interaction. The hypothesis was tested in a 36-year-old woman who was maintained on lithium carbonate 300 mg four times daily and required cisplatin for cancer of the tongue. The lithium dose was kept constant. cisplatin was given at 100 mg/m <sup>2</sup> and followed by i.v. mannitol and

<i>Combination</i>	<i>Interaction</i>
	fluids. The serum lithium fell from 1.0 to 0.3 mEq/l during the first course and from 0.8 to 0.5 mEq/l during the second. These decreases were transient being reversed in 2 days. The relative contribution of the cisplatin and the forced diuresis to the presumed increase in lithium clearance is unknown.
	There are theoretical reasons and some clinical evidence to indicate that serum lithium levels fall when cisplatin is given. This effect appears to be rapidly reversed but may be important when high-dose cisplatin is repeated frequently. Lithium levels should be carefully monitored under such circumstances.
<b>Cisplatin/sodium bisulphite (57)</b>	Cisplatin reacts chemically with the antioxidant, sodium bisulphite; cisplatin may be inactivated if added to solutions containing this antioxidant.
<b>Colaspase/antidiabetic agent (58–60)</b>	Colaspase causes significant impairment of glucose tolerance and is diabetogenic (59, 60). It would therefore be expected to antagonize the actions of insulin and oral hypoglycaemic drugs. Use with care in the diabetic patient and check frequently for continued diabetic control.
<b>Dacarbazine/ hydrocortisone (61)</b>	Dacarbazine is incompatible with hydrocortisone sodium succinate in solution; it forms an immediate precipitate.
<b>Ethoglucid/plastic materials (62)</b>	Concentrated solutions of ethoglucid react with plastics. Glass syringes should be used for such solutions.
<b>Interleukin-2/NSAIDs e.g. indomethacin (63) ibuprofen (64)</b>	Administration of indomethacin to patients receiving interleukin-2 led to severe weight gain, oliguria and azotaemia. Conversely, ibuprofen has been reported to reduce interleukin-2 toxicity especially fever, chills, nausea and vomiting.
<b>Pentostatin/allopurinol (65)</b>	Hypersensitivity vasculitis resulting in death has been attributed to the use of pentostatin with allopurinol. The combination is contraindicated.

<i>Combination</i>	<i>Interaction</i>
<b>Procarbazine/alcohol (66)</b>	Procarbazine inhibits aldehyde dehydrogenase and produces an 'Antabuse-like' reaction. Patients should be warned of the possibility of developing intolerance to alcohol.
<b>Procarbazine/CNS acting drugs (66)</b> e.g. barbiturates narcotics (e.g. pethidine (meperidine)) phenothiazine derivatives tricyclic antidepressants	Procarbazine is a MAOI and therefore interacts with barbiturates slowing their metabolism and prolonging their duration of action. The effect of narcotics may also be prolonged. Combination with phenothiazines may lead to hypertension and increased extrapyramidal reactions. Since MAOIs block enzymes normally metabolizing tricyclic compounds, their combination may evoke serious reactions.
	Combinations of these drugs with procarbazine are best avoided. Hypertensive crisis, if it occurs, should be treated with the $\alpha$ -adrenergic blocking drug phentolamine.
<b>Procarbazine/sympathomimetic amines and tyramine-containing foodstuffs (66)</b> e.g. avocado pears broad-bean pods beers Bovril canned figs caviar unprocessed cheese (especially Cheddar and Gruyère) Chianti wine and sherry game liver New Zealand prickly spinach pickled herring yeast products (including Marmite)	Procarbazine is a MAOI and therefore interactions with sympathomimetic amines and with foodstuffs rich in tyramine may occur as with other MAOIs. Combination of these amines or foodstuffs with procarbazine is best avoided. Hypertensive crisis, if it occurs, should be treated with the $\alpha$ -adrenergic-blocking drug phentolamine.

<i>Combination</i>	<i>Interaction</i>
<b>Tamoxifen/allopurinol</b> (67)	Mild chronic allopurinol hepatitis has been reported to have been exacerbated by tamoxifen.
<b>Tamoxifen/warfarin</b> (68-71)	A marked potentiation of warfarin by tamoxifen has been reported on a number of occasions. In several cases the interaction has been life threatening with increased prothrombin times, haematuria, and haematoma. Peliosis, hepatitis and fatal liver haemorrhage has been reported in one case who was receiving both warfarin and a thyroxine-liothyronine preparation.

## VI. GENERAL INTERACTION ISSUES

### 1. Inappropriate ADH Secretion During Cancer Chemotherapy

<i>Combination</i>	<i>Interaction</i>
<b>Oncological agent/other drugs affecting ADH secretion</b> (72) e.g. amitriptyline (73) carbamazepine (74) chlorpropamide (75-80) clofibrate (81) cyclophosphamide (82) diuretics (83) fluphenazine (84) haloperidol (85) vinblastine (87) vincristine (88-89)	A drug-induced syndrome of inappropriate secretion of antidiuretic hormone has been described secondary to both cyclophosphamide or vincristine therapy or combinations containing them. There are other reports of this syndrome complicating chlorpropamide therapy both in patients with diabetes mellitus (75-77) and in patients with diabetes insipidus (78-80). The syndrome has also been described as occurring with amitriptyline, carbamazepine, clofibrate, diuretics, fluphenazine, haloperidol, thiothixene, thioridazine and vinblastine. Combination of any of these drugs might be expected to increase the likelihood of the syndrome occurring with resulting water retention and natriuresis. Treatment with any combination of these drugs should be used with caution and the syndrome of water intoxication should be borne in mind when any patient presents with symptoms of drowsiness, headaches, anorexia, nausea, vomiting, depression and confusion.

### 2. Resistance to Antineoplastic Agents

Resistance to antineoplastic agents is one of the greatest limitations to the use of chemotherapy in malignant disease. Resistance may be intrinsic to the tumour or acquired during the course of therapy. Much interest has surrounded the discovery

that certain drugs can modulate or inhibit the mechanisms of resistance. In particular compounds such as verapamil, quinidine, and cyclosporin which have the ability to block the p-glycoprotein pump, which acts as an efflux pump for a range of cytotoxic substances and which is responsible for multi-drug resistance (90, 91).

The classes of drugs which it is claimed have some ability to modulate multi-drug resistance include: (i) calcium channel blockers including verapamil, nifedipine, nicardipine; (ii) various phenothiazines, thioxanthines, trifluoperazine, and flupenthixol; (iii) tamoxifen; (iv) cyclosporin; (v) various anti-arrhythmic agents, amiodarone, propranolol, quinidine (92).

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# **CHAPTER 9**

**Drug Interactions with Aspirin and Other  
Non-Steroidal Anti-Inflammatory Agents**

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## **9.1. ASPIRIN**

### **INTRODUCTION**

The inclusion of a separate table of drug interactions with aspirin (acetylsalicylic acid) is dictated by the enormous usage of this non-prescription drug alone as an antipyretic, analgesic and anti-inflammatory agent, or as a component in a wide spectrum of combination products. A comprehensive list of official and proprietary aspirin and aspirin-containing preparations is listed in *Martindale, The Extra Pharmacopoeia*, 31st edition (1996). The major adverse effects of aspirin are due to its gastric irritant effects, its interference with platelet function, and in allergic subjects it produces angioneurotic oedema, urticaria and bronchoconstriction. There is considerable cross-reactivity between aspirin and other NSAIDs especially in these hypersensitivity reactions.

The use of aspirin in children under the age of 12 years is extremely limited because of the risk of Reye's syndrome which is characterized by acute encephalopathy and fatty degeneration of the liver. Several large studies as well as individual case reports have found an association between Reye's syndrome and the prior ingestion of aspirin (1-6). Consequently, the use of aspirin in children as a general analgesic and antipyretic is no longer considered to be justified. Paracetamol is the acceptable alternative. Most authorities consider that one of the few acceptable indications remaining for aspirin in children is in the treatment of juvenile rheumatoid arthritis.

Aspirin has valuable use as secondary prophylaxis to reduce the risk of myocardial infarction or cardiovascular events such as stroke in patients at risk.

### **INTERACTIONS**

Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol. Concurrent administration of aspirin and dipyridamole may result in raised peak plasma salicylate levels and an increased area under the time-concentration curve (AUC) for the salicylate. Administration of aspirin together with carbonic anhydrase inhibitors (e.g. acetazolamide), metoclopramide, or the  $\beta$ -blocker, metoprolol, may elevate salicylate plasma concentrations to toxic levels. Salicylate concentrations in patients with rheumatoid arthritis may be reduced by concurrent corticosteroids but may be raised to toxic levels if corticosteroids are withdrawn. Antacids and adsorbents may increase the excretion of aspirin in alkaline urine. Aspirin may enhance the activity of coumarin anticoagulants, methotrexate, phenytoin,

sulphonylurea hypoglycaemics, and valproic acid. Aspirin diminishes the effects of uricosuric agents such as probenecid and sulphinpyrazone. It may diminish the plasma concentrations of some other NSAIDs, for example fenbufen, indomethacin and piroxicam. Drug interactions involving aspirin have been reviewed (7) and are detailed in the following Table of Drug Interactions.

<i>Combination</i>	<i>Interaction</i>
<b>Aspirin/ACE-inhibitor</b>	Aspirin and other NSAIDs have been reported to reduce or abolish the hypotensive action of ACE-inhibitors. It has been proposed that part of the action of ACE-inhibitors is prostaglandin-dependent which might explain this interaction with drugs that block prostaglandin synthesis. The precise mechanism is, however, uncertain (8–10). The possibility of an interaction between aspirin and ACE-inhibitors, especially in patients with heart failure, has been investigated but data on the interaction are inconclusive (11).
<b>Aspirin/alcohol</b>	Aspirin damages the gastric mucosa and can cause bleeding; furthermore there is good evidence that alcohol can increase this blood loss (12, 13). This interaction is not specific for aspirin and it also occurs with alcohol and NSAID combinations. The combination of aspirin and alcohol must clearly be avoided in any patient who has had a aspirin-induced gastrointestinal haemorrhage. The impairment of haemostasis may underlie otherwise unexplained episodes of bleeding.
<b>Aspirin/anticoagulant (14–16)</b>	Aspirin displaces coumarins from plasma protein binding sites and thus potentiates their anticoagulant action. Aspirin also tends to reduce plasma prothrombin when taken in large doses. It decreases platelet adhesiveness and has an ulcerogenic effect leading to occult bleeding from superficial gastric erosions; haemorrhage is made worse if anticoagulant drugs and aspirin are taken together. However, aspirin-induced blood loss may be reduced by administering aspirin as an enteric coated or modified-release tablet. Otherwise aspirin should be avoided by patients taking anticoagulants.

<i>Combination</i>	<i>Interaction</i>
<b>Aspirin/calcium channel blocker</b>	The antiplatelet effects of aspirin and calcium-channel blockers may be increased when they are used together. There have been isolated reports of disturbed haemostasis including abnormal bruising, prolonged bleeding times and ecchymosis (17, 18). The combination should be used with caution.
<b>Aspirin/corticosteroid (19, 20)</b>	Corticosteroids decrease the blood salicylate concentration by increasing the glomerular filtration rate. Decreasing corticosteroid dose in patients on aspirin may increase serum salicylate concentrations and patients should be watched for symptoms of salicylism. It must be noted that salicylates and corticosteroids are both ulcerogenic.
<b>Aspirin/griseofulvin</b>	Plasma salicylate concentrations in an 8-year-old child receiving long-term aspirin therapy for rheumatic heart disease were markedly reduced when griseofulvin treatment was started (21). It was suggested that griseofulvin might interfere with the absorption of aspirin.
<b>Aspirin/insulin and hypoglycaemic agents (22–25)</b>	<i>In vitro</i> studies have shown aspirin to displace tolbutamide and chlorpropamide from plasma protein binding thus increasing unbound active sulphonylurea. The insulin requirement of diabetics can also be reduced by aspirin. Cases have been reported where aspirin has contributed to profound hypoglycaemia in patients on sulphonylureas, however, in general the interaction appears to be rare and gives little trouble.
<b>Aspirin/methotrexate (26, 27)</b>	Methotrexate can be displaced from its plasma protein binding by salicylates. In addition, salicylates appear to exhibit renal tubular excretion of methotrexate by about 35%. This interaction could increase methotrexate toxicity. See also NSAID/methotrexate interactions in the following section.
<b>Aspirin/other NSAIDs phenylbutazone</b>	Phenylbutazone inhibits the uricosuria which usually follows large doses of salicylate (28, 29). In a study involving four patients with gout, uricosuria had

<i>Combination</i>	<i>Interaction</i>
<b>Aspirin/other NSAIDs</b> <i>phenylbutazone cont.</i>	followed aspirin 5 gm/day. Over the next 3-day period, 200, 400 and 600 mg dosages of phenylbutazone caused the serum level urate level to rise from 4–6 mg/100 ml (28, 29).
<b>Aspirin/tenoxicam</b>	Simultaneous administration of high-dose aspirin was investigated on the pharmacokinetics of single and multiple doses of tenoxicam on normal subjects (30). Aspirin caused a 24% drop in the $t_{1/2}$ value, a 49% rise in the volume of distribution, and a 98% increase in the clearance of tenoxicam. Steady-state concentrations of tenoxicam decreased significantly from 10.4 to 4.5 $\mu\text{g}/\text{ml}$ in the presence of chronic, high-dose aspirin. These effects were consistent with a competitive protein binding interaction. Concurrent aspirin caused significant reduction in plasma tenoxicam concentrations. This result is in agreement with many studies of the interaction of other NSAIDs with aspirin (31), and adds weight to the general view that there is little rationale for the combination of an NSAID and aspirin in the treatment of rheumatic diseases.
<b>Aspirin/phenytoin</b> (32–36)	Aspirin displaces phenytoin from binding sites, but acute interaction of aspirin and phenytoin is unlikely to be clinically significant because the increased free phenytoin level is compensated by increased availability of the drug for metabolic pathways and more rapid clearance. The overall result of the interaction is a decrease in the serum level of total (free plus bound) phenytoin with little change in the free drug level. There could be complications if the interaction occurred in a patient treated chronically with the aspirin–phenytoin combination. The interaction might then interfere not only with the plasma protein binding but also with drug metabolism. Normally, however, the interaction does not necessitate modification of phenytoin dosage.

<i>Combination</i>	<i>Interaction</i>
<b>Aspirin/probenecid</b> (28, 29, 37-39)	Salicylates antagonize the uricosuric action of probenecid and sulphapyrazone and should not be given concurrently. This interaction is exceptionally well documented for both drugs and is of considerable significance. Aspirin should not be taken during the treatment of gout with either drug.
<b>Aspirin/spironolactone</b>	A study on six subjects showed that 600 mg aspirin reversed the natriuresis induced by spironolactone. It has been suggested that aspirin might displace spironolactone as a competitor with aldosterone at the renal tubular receptor site (42). Any real significance of this interaction is doubtful since spironolactone is most often given in conjunction with other diuretics (e.g. thiazides) to prevent potassium depletion.
<b>Aspirin/sodium valproate</b>	In five of six epileptic children taking valproic acid 18-49 mg/kg daily, the steady-state serum free fractions of valproic acid rose from 12 to 43% when antipyretic doses of aspirin were also taken (43). Mean total valproic acid half-life rose from 10.4 to 12.9 hr and mean free valproic acid rose from 6.8 to 8.9 hr when salicylate was present in the serum. Salicylate appeared to displace valproic acid from serum albumin <i>in vitro</i> , but increased valproic acid half-life and changes in valproic acid elimination patterns suggested that serum salicylate had also altered valproic acids metabolism. Although no untoward effects were noticed, results suggest that prolonged use of aspirin with valproic acid may result in greater than anticipated free levels of valproic acid with cumulation to toxic levels. A related study in children also confirmed that aspirin (up to 68 mg/kg daily) caused decreased clearance of free fraction and 49% increase in free serum levels of valproate without apparent untoward effects.(44). Co-administration of these drugs for more than 24 hr might result in toxic levels of valproic acid due to competition for active transport sites in renal tubules or liver (44). Although no untoward effects were seen in these studies, the results strongly suggest that this combination should be avoided if possible, certainly for any prolonged course of treatment with salicylates.

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## 9.2. OTHER NSAIDs

### INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are thought to act through inhibition of cyclooxygenase-1 and -2 (Cox-1 and Cox-2) which are involved in the synthesis of prostaglandins. Cox-1 is associated with adverse gastrointestinal effects, whilst Cox-2 is associated with anti-inflammatory activity (45–47). Hence the interest in highly selective inhibitors of Cox-2; meloxicam and nimesulide are two such drugs.

Many NSAIDs possess centres of chirality within their molecular structure, with different chiral forms (enantiomers) having different degrees of pharmacological activity (48). The chirality of a drug may have subtle effects on its toxicity and interactions.

Prostaglandins have an important role in the production of pain, inflammation and fever and NSAIDs therefore find their main use as analgesics, antipyretics and anti-inflammatory agents. In single doses, NSAIDs have analgesic activity comparable to that of paracetamol, although paracetamol is preferred especially in the elderly. In regular full dosage NSAIDs have both a lasting analgesic effect and an anti-inflammatory action which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation. NSAIDs are more appropriate than paracetamol or opioid analgesics in the inflammatory arthritides (e.g. rheumatoid arthritis and some cases of advanced osteoarthritis). They may be of some value in the less well defined conditions of back-pain and soft-tissue disorders.

The following NSAIDs are in common clinical use in the UK:

aceclofenac	indomethacin
acemetacin	ketoprofen
aspirin	<b>ketorolac trometamol</b> (see CSM restrictions on dose and duration of treatment (48)).
azapropazone*	mefenamic acid
benorylate	nabumetone
diclofenac	naproxen
piroxicam	phenylbutazone**
diflunisal	piroxicam
etodolac	sulindac
fenbufen	tenoxicam
fenoprofen	tiaprofenic acid

**flurbiprofen  
ibuprofen****tolmetin**

\* Azapropazone has been restricted in the UK by the CSM for use in rheumatoid arthritis, ankylosing spondylitis and acute gout only when other NSAIDs have been tried and failed. The CSM has also reminded of the need to advise patients taking azapropazone to avoid direct exposure to sunlight or to use sunblock preparations.

\*\* Phenylbutazone is a potent anti-inflammatory drug but because of occasional serious blood dyscrasias its use in the UK is limited to the hospital treatment of ankylosing spondylitis.

Although there have been many studies comparing the efficacy of one NSAID with one or several others there has been no wide-ranging comparison between all NSAIDs to allow them to be ranked in order of efficacy. Generally it is felt that there is little difference in anti-inflammatory activity between them, and the choice is largely empirical. There has, however, been a recent evaluation by the CSM of the safety of seven NSAIDs which has indicated that differences exist in the risks of serious upper gastrointestinal side effects (49). Azapropazone is associated with the highest risk and ibuprofen with the lowest. Piroxicam, ketoprofen, naproxen and diclofenac are associated with intermediate risks (possibly higher with piroxicam). There are insufficient data to reach clear conclusions on the other available oral NSAIDs.

Apart from their adverse effects on the gastrointestinal tract (peptic ulceration and its complications of perforation and bleeding), other serious reactions are those involving the kidney and liver, blood disorders and allergy (e.g. anaphylaxis), which although less common are also important. CNS-related side effects include headache, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally, and include fever, asthma, and rashes. In respect of asthma the CSM has warned that any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter (50). Due to the increased susceptibility of the elderly to the side effects of NSAIDs, the CSM has previously warned that NSAIDs should be given to them only after other forms of treatment have been considered. NSAIDs are contra-indicated in patients with a past history of peptic ulceration.

There is considerable variation in individual patients response to such drugs. About 60% of patients will respond to any NSAID, of the others, those who do not respond to one may well respond to another. An analgesic effect should normally be obtained within 1 week, whereas an anti-inflammatory effect may not be achieved for up to 3 weeks. If appropriate responses are not obtained within these times then another NSAID should be tried.

## **INTERACTIONS**

Notable interactions involving NSAIDs include possible enhancement of the effects of oral anticoagulants and increased plasma concentrations of lithium, methotrexate and cardiac glycosides. The risk of nephrotoxicity may be increased if given with

ACE-inhibitors, cyclosporin or diuretics. There may also be an increased risk of hyperkalaemia with ACE-inhibitors and potassium-sparing diuretics. The antihypertensive effect of some agents including ACE-inhibitors,  $\beta$ -blockers and diuretics may be reduced. Convulsions may occur due to an interaction with quinolone antibacterials. NSAIDs may enhance the effect of phenytoin and sulphonylurea antidiabetics. The concomitant use of more than one NSAID should be avoided because of the increased risk of adverse effects. The risk of gastrointestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids. Some NSAIDs can interfere with thyroid function tests by lowering serum thyroid hormone concentrations. These and other interactions involving NSAIDs are described in the following Table of Drug Interactions (see also review article (51)).

<i>Combination</i>	<i>Interaction</i>
<b>NSAID/antacid (52)</b>	In fasting normal subjects, aluminium hydroxide gel decreased the peak plasma concentration of diflunisal by 46%, the AUC by 26% and the urinary recovery by 14%. In contrast, magnesium hydroxide suspension (in the fasting state) increased early peak diflunisal concentrations by 54% at 1 hr and 130% at 5 hr, and increased the AUC by 10%. In the postprandial state antacid, alone or combined, had no effect on diflunisal bioavailability.
<b>NSAID/antidiabetic agents (53, 54)</b>	Some anti-inflammatory agents and analgesics, including azapropazone (53), phenylbutazone (55), and salicylates (56), may increase the hypoglycaemic effects of sulphonylureas and may necessitate a reduction in their dosage requirements.
<b>NSAID/antihypertensive</b>	The antihypertensive effects of some agents, including ACE-inhibitors, $\beta$ -blockers and diuretics (see below) may be reduced by concomitant administration of NSAIDs. Indomethacin has been shown to interfere with the hypotensive effects and the renin-stimulating effects of captopril in normal subjects (57) and also to reduce the hypotensive effect of oxprenolol by about 50% in patients with essential hypertension (58). These interactions are thought to be due to the inhibition of prostaglandin synthesis which is thought to have a role in the action of these antihypertensives. Caution should be exercised when NSAIDs are given to patients receiving anti-hypertensive treatment.

<i>Combination</i>	<i>Interaction</i>
<b>NSAID/appetite suppressant</b>	<p>Severe systemic hypertension developed in a patient who took indomethacin shortly after ingesting an appetite suppressant (<i>Trimolets</i>) containing phenylpropanolamine. The mechanism of this interaction was explained by indomethacins inhibition of prostaglandin synthesis evoking enhanced sympathomimetic effects of phenylpropanolamine (59). An additional study showed that the ingestion of a single dose of a phenylpropanolamine-containing appetite suppressant (<i>Trimolets</i>) or decongestant (<i>Contac 500</i>)* caused a significant hypertensive response to corticosteroid therapy in, respectively, 12/37 and 4/34 subjects. Twenty of the subjects taking Trimolets reported adverse side effects (60).</p> <p>* <i>Contac 500</i> formulation in Australia is equivalent to <i>Contac 400</i> formulations elsewhere.</p>
<b>NSAID (diclofenac)/cyclosporin misoprostol</b>	<p>Deterioration in renal function has been reported after the concomitant use of diclofenac and cyclosporin (61). The AUC of diclofenac was reduced by some 20% when it was given as a single 100-mg daily dose in the form of a modified release preparation to subjects also receiving misoprostol 800 µg daily. Concomitant administration was also associated with an increase in severity and incidence of gastrointestinal effects. Studies by the manufacturer with this combination failed to find any significant pharmacokinetic interaction (62).</p>
<b>NSAID/cholestyramine colestipol</b>	<p>Cholestyramine reduced the bioavailability of diclofenac when the two agents were given together, and colestipol produced a similar but smaller effect (63).</p>
<b>NSAID/diagnostic test</b>	<p>The presence of metabolites of etodolac in the urine may give rise to a false positive reaction for bilirubin (64). False-negative results in the dexamethasone suppression test have been reported in patients taking indomethacin (65). Some NSAIDs can interfere with thyroid function tests by lowering serum thyroid hormone concentrations (66).</p>

<i>Combination</i>	<i>Interaction</i>
<b>NSAID/diuretic (67–74)</b>	<p>There are many early reports of interaction between diuretics and NSAIDs. Indomethacin, in particular, has been shown to attenuate or abolish the diuretic and hypotensive effects of thiazide and loop diuretics. Piroxicam is also known to have this effect and is contraindicated in elderly patients with cardiac failure. Reversible acute renal failure occurred in four patients during dosage with indomethacin and triamterene. Renal function was unaltered when each agent was administered alone. It has been suggested that prostaglandin unmasks the nephrotoxic potential of triamterene (75). Deterioration of renal function has been reported with diclofenac and triamterene (76). The mechanism involved in these interactions may be an interference with the production of renal prostaglandins which are required to mediate the action of the diuretics. This appears to be a class effect of the NSAIDs. However, not all members have been tested and there appears to be differences between the different NSAIDs in this respect. Thus flurbiprofen was found to have less effect than indomethacin on the diuresis produced by frusemide. It has been suggested that sulindac may be an exception to this general rule. It has been shown not to inhibit frusemide-induced renin release or natriuresis. This may be because sulindac is itself a prodrug that is metabolized to an active sulphide which is variably but irreversibly converted to an inactive sulphone – thus, renal metabolism may be protective. Apart from possible variations between NSAIDs, patients will be sensitive to this interaction depending on their degree of cardiac failure, age, renal function, etc. NSAIDs are generally contraindicated in patients requiring treatment with diuretics.</p>
<b>NSAID (topical)/eye drops</b>	<p>The manufacturer of acetylcholine ophthalmic preparations has stated that there have been reports that acetylcholine and carbachol have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs (77).</p>

	<i>Combination</i>	<i>Interaction</i>
<b>NSAID/lithium diclofenac</b>		In five normal women, diclofenac (50 mg tid for 7–10 days) reduced the renal clearance of lithium (12 mEq bid) resulting in a clinically important increase (26%) in steady-state plasma lithium concentration. This effect may be associated with an inhibition of prostaglandin synthesis since diclofenac also reduced the urinary excretion of dinoprostone (prostaglandin E <sub>2</sub> ) by about 50% compared with placebo (78).
<b>Indomethacin</b>		Indomethacin increased plasma lithium concentrations by 59% in psychiatric patients and by 30% in normal subjects. Renal clearance was reduced by 31% in the group as a whole. Prostaglandin synthesis was reduced by 55% suggesting that renal clearances of lithium may be affected by a prostaglandin-dependent mechanism possibly in the distal renal tubule (79).
<b>NSAID/methotrexate azapropazone</b>		Severe, and in some cases fatal, aggravation of methotrexate toxicity has been reported when it was administered with various NSAIDs (80–85) including azapropazone (82), aspirin and other salicylates (80, 81). The mechanism is uncertain but may include both displacement of methotrexate from protein-binding sites or an effect of NSAIDs on the kidney resulting in reduced methotrexate excretion (85, 86).
<b>Indomethacin</b>		One patient has been reported to suffer acute renal failure due to the concomitant action of methotrexate and indomethacin (87). The mechanism was suggested to be an indomethacin-induced inhibition of renal prostaglandin (PGE <sub>2</sub> ) synthesis which would decrease vasodilatation. The inhibition of renin release is also dependent upon PEG <sub>2</sub> . These two together would decrease the renal perfusion of methotrexate. There is a further possibility that a biotransformation of methotrexate and indomethacin in the liver could produce a combination which is not easily eliminated by the kidneys. An earlier report described two patients who suffered fatal acute renal failure when receiving sequential intermediate-dose methotrexate

<i>Combination</i>	<i>Interaction</i>
	<p>and 5-fluorouracil therapy to which indomethacin was added (88).</p>
<b>Ketoprofen</b>	<p>Two cases of lethal methotrexate toxicity have been reported in patients who were also taking ketoprofen (89); 118 cycles of high-dose methotrexate given to 36 patients over 5 years were also examined retrospectively to estimate the number with severe toxicity and to assess the role of ketoprofen or other NSAIDs in this toxicity.</p> <p>Of the 36 patients (118 cycles), 24 patients (104 cycles) were free of toxicity; five patients (five cycles) were associated with WHO classification grade I-II toxicity and nine patients (nine cycles) with grade III-IV toxicity. Co-administration of ketoprofen was found in four of these nine patients which were characterized by severe methotrexate toxicity; of the remaining five cases, of severe methotrexate toxicity, one was associated with concomitant dosage of another NSAID, diclofenac (83).</p>
<b>Diclofenac</b>	<p>The simultaneous administration of high-dose methotrexate and ketoprofen was associated with prolonged and striking enhancement of serum methotrexate levels. The mechanism of the interaction was thought to be inhibition of renal prostaglandin synthesis by ketoprofen which would decrease renal perfusion rate and thus inhibit methotrexate clearance. An alternative was competitive renal secretion of the two drugs. The authors of this report warned that a severe interaction might be anticipated with other NSAIDs.</p>
<b>Naproxen</b>	<p>One case has been reported of a fatality attributed to a methotrexate-naproxen interaction after the administration of low-dose methotrexate (2.5 mg, 12 hourly, planned for three consecutive doses weekly) together with conventional doses of naproxen. The elderly patient with rheumatoid arthritis unresponsive to penicillamine and gold, developed fever and diarrhoea within 24 hr of receiving the combination. The patient was admitted to hospital and died. The cause of death</p>

*Combination**Interaction***Naproxen cont.**

was attributed to an interaction between methotrexate and naproxen and was complicated by an apparent overdose of methotrexate by the patient (90).

Evidence has accumulated over the last few years that the use of NSAIDs alone can produce a variety of untoward renal effects. The most common form is acute renal failure resulting from haemodynamic changes secondary to the inhibition of prostaglandin synthesis. Elderly patients are at greatest risk. At the request of the CSM, all data sheets for NSAIDs now include a statement that these drugs can cause renal toxicity (91).

Despite the risks, methotrexate and NSAIDs are frequently prescribed together in the treatment of rheumatoid arthritis (92, 93), and provided this is done with caution in low doses, and patients are monitored and cautioned to avoid additional over-the-counter analgesics, such combinations need not be contraindicated. There is also an opposing view that the use of any NSAID with methotrexate is not justified in view of the unacceptable, possibly fatal, toxicity that it may produce. This has already been demonstrated with four NSAIDs.

**Flurbiprofen****Ketoprofen****Piroxicam**

However, a recent study in patients given low doses of methotrexate for rheumatoid arthritis suggested that flurbiprofen, ketoprofen or piroxicam given concomitantly did not influence methotrexate toxicity (94).

**NSAID/NSAID**

Concurrent administration of anti-inflammatory doses of aspirin increased indomethacin blood concentrations by about 20%. Administration of indomethacin with diflunisal decreased the renal clearance and increased the plasma concentration of indomethacin. Combined use of indomethacin and diflunisal has resulted in fatal gastrointestinal haemorrhage therefore these drugs should not be used concurrently (65).

**NSAID/phenytoin**

Various analgesics and anti-inflammatory agents have been reported to interact with phenytoin.

<i>Combination</i>	<i>Interaction</i>
<b>Azapropazone</b>	Azapropazone appears to be a competitive inhibitor of phenytoin metabolism and has also been implicated in interactions resulting in toxicity (95, 96).
<b>Ibuprofen</b>	There is a single report of toxicity in a patient receiving ibuprofen with phenytoin (97); however, in a study in nine healthy subjects, ibuprofen had no effect on the pharmacokinetics of phenytoin (98).
<b>Phenylbutazone</b>	Phenylbutazone has been reported to cause an initial decrease in serum phenytoin, followed by an increase (99); in addition to its effects on protein binding, it inhibits phenytoin metabolism (100) and severe phenytoin toxicity may result (101).
<b>NSAID (diflunisal)/ probenecid</b>	Average steady-state plasma concentrations of diflunisal were increased by 65% when it was administered with probenecid (102). This was due mainly to reduced formation of phenolic and acyl glucuronides. However, probenecid reduced their renal clearance so plasma concentrations of these glucuronides and also the sulphate conjugate increased. Plasma concentrations of indomethacin are also likely to be increased in patients receiving indomethacin, ketoprofen or naproxen.
<b>NSAID/quinolone antimicrobial</b>	Convulsions may occur due to an interaction between the quinolones and NSAIDs. Three such interactions have been reported to the CSM, who have urged caution when considering the use of a quinolone in patients with a history of convulsions or epilepsy and in those who are already receiving a NSAID. In this respect it is important to note that the epileptogenic potential of the quinolone group of antimicrobials has long been recognized. The CSM has received 26 reports of convulsions associated with the use of ciprofloxacin, one case with norfloxacin and one case with ofloxacin. The reactions can occur in patients known to have epilepsy and in those with no previous history of convulsions. (91).
<b>NSAID/various drugs in solution</b>	Indomethacin sodium injection is reconstituted with preservative-free sodium chloride or water for injection. It is incompatible with preparations

<i>Combination</i>	<i>Interaction</i>
<b>NSAID/other drugs in solution cont.</b>	containing glucose, and reconstitution at a pH (below 6) may cause precipitation of indomethacin. Visual incompatibility, possibly due to low pH below 6, has been reported between indomethacin sodium injection and tolazoline hydrochloride (103), 7.5 and 10% glucose injection, calcium gluconate, dobutamine, dopamine, cimetidine (104), gentamicin sulphate and tobramycin sulphate (105).
<b>NSAID/warfarin (106–108)</b>	<p>NSAIDs should be used with caution, or not at all, in patients on warfarin or other anticoagulant. Many NSAIDs inhibit platelet function to some extent and have an irritant effect on the gastrointestinal tract, so increasing the risk of haemorrhage. Furthermore, some NSAIDs increase the hypoprothrombinaemic effect of warfarin possibly by an intrinsic effect on coagulation or by displacement of warfarin from plasma protein binding sites. Many <i>in vitro</i> studies have attempted to compare the relative displacing action of a range of NSAIDs, but the results cannot easily be extrapolated into the clinical situation. Changes in plasma concentration of unbound warfarin resulting from displacement interactions are most likely to occur in the first few weeks after an NSAID is added to, or withdrawn from, warfarin therapy; monitoring of anticoagulant therapy is therefore critical during this time.</p> <p>Concurrent administration of phenylbutazone and warfarin has led to serious haemorrhage and should be avoided. This NSAID effects the metabolism of the R- and S-isomers of warfarin in complex and different ways with the net effect of enhancing its anticoagulant activity (109). Other NSAIDs, e.g. oxyphenbutazone, azapropazone (110–112) and feprazone (113) behave similarly and these combinations should also be avoided.</p> <p>For the following NSAIDs, there are a few studies or isolated reports suggesting that they may enhance the hypoprothrombinaemic effect of warfarin or other specified anticoagulant: diflunisal and nicoumalone (114) on warfarin (115); flurbiprofen and nicoumalone (116), indomethacin (117, 118), ketoprofen (119),</p>

*Combination**Interaction*

meclofenamate sodium (120), mefenamic acid (121), piroxicam (122), sulindac (107, 108), tiaprofenic acid (with nicoumalone) (123), and tolmetin sodium (124). In many cases the result of the interaction was an increased prothrombin time which may or may not be clinically significant; in other cases haemorrhage occurred. For many of the above NSAIDs, particularly indomethacin, there are also studies which failed to show any enhancement of warfarin's activity. NSAIDs with apparently minimal activity on warfarin's activity include etodolac, ibuprofen, naproxen and tenidap (125). In view of these considerations, NSAIDs should not be used and paracetamol is recommended as the general analgesic and antipyretic for patients receiving anticoagulant therapy. There is, however, still a risk of bleeding in patients taking regular doses of paracetamol whilst receiving anticoagulants (126).

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# CHAPTER 10

## Drug Interactions with Vaccines and Interferons

Vaccines are defined as preparations of antigenic materials which are administered with the object of inducing in the recipient a specific active immunity to specific bacteria or viruses. They may contain living or killed micro-organisms or bacterial toxins or toxoids; vaccines may be simple vaccines prepared from a single species or strain or mixed vaccines involving a mixture of one or more species or strains. Interactions between a vaccine and a drug have so far been reported for a limited number of drugs.

Bacillus Calmette-Guérin (BCG) vaccine (1), endotoxin (2), interferon-inducing agents (3), and interferon itself (4), depress cytochrome P450 activity in laboratory animals. The induction of interferons are thought to be the cause of a number of reported vaccine drug interactions in man.

The second group of vaccine/drug interactions relate to immunosuppressive or corticosteroid therapy. In this context the following general advice should be followed.

- (a) Live vaccines should not be given during corticosteroid therapy or cancer chemotherapy or immunosuppressive therapy. Administration of live vaccines should be postponed for 3 months after stopping corticosteroid therapy or 6 months after stopping cancer chemotherapy or immunosuppressive therapy.
- (b) Live vaccines should not be administered to pregnant women.
- (c) If exposure to measles or other infectious disease has taken place in circumstances (a) or (b) above the use of appropriate immunoglobulins may be acceptable.

- (d) The use of vaccines in HIV-positive subjects has been the subject of guidance from the British Department of Health:
- (i) HIV-positive patients may be given the following live vaccines: measles, mumps, poliomyelitis and rubella. They may be given the following inactivated vaccines: cholera, diphtheria, *Haemophilus influenzae* type b, meningococcal, tetanus, typhoid (injection).
- (ii) HIV-positive subjects **should not** receive BCG, yellow fever, typhoid (oral). If live poliomyelitis vaccine is given to HIV-positive patients they continue to excrete live virus in their faeces for longer than normal subjects.
- (e) *Haemophilus influenzae* B vaccine is not a live vaccine and can be used in immuno-compromized children. Vaccination need not be postponed because of a minor illness without fever or systemic upset. Previous invasive *Haemophilus influenzae* B infection may not induce immunity in those under 2 years, so immunization is still recommended (5, 6).

## INTERFERONS

Interferons are naturally occurring proteins with complex effects on immunity and cell function. Interferons  $\alpha$ ,  $\beta$  and  $\gamma_{1b}$  are commercially available.

Interferons are produced naturally within the body in response to antigenic challenge particularly viral infections. While  $\alpha$ -,  $\beta$ - and  $\gamma$ -interferons share certain properties, interferon  $\gamma_{1b}$  has potent phagocyte-activating properties not seen with the other interferons (7).

**Interferon  $\alpha$**  is used in the treatment of hairy-cell leukaemia, recurrent or metastatic renal cell carcinoma, AIDS-related Kaposi's sarcoma, chronic active hepatitis B, chronic hepatitis C, chronic myelogenous leukaemia, condylomata acuminata and cutaneous T-cell lymphoma.

Interferon  $\alpha$  has been shown to affect oxidative metabolic processes and to reduce the metabolic clearance of theophylline.

**Side effects:** the most frequently reported symptoms are those of a 'flu-like' illness; depression and suicidal behaviour, myelosuppression, cardiovascular effects and hepatotoxicity have been reported.

**Interferon  $\beta$**  has recently been approved by a number of national drug regulatory authorities for use in patients with relapsing *multiple sclerosis* (characterized by at least two attacks of neurological dysfunction over the previous 2-year period, followed by complete or incomplete recovery).

Interferon  $\beta$  should not be used in patients with a history of severe depressive illness, inadequately controlled epilepsy or hepatic impairment.

**Interactions:** Interferon beta does not appear to affect hepatic drug metabolism.

**Side effects** include reactions at injection site, flu-like symptoms, and occasionally hypersensitivity reactions (e.g. bronchospasm, anaphylaxis and urticaria), depression and anxiety, and convulsions.

**Interferon  $\gamma_{1b}$**  is used as an adjunct to antibiotics to reduce frequency of serious infection, i.e. patients with chronic granulomatous disease.

**Side effects:** the most commonly reported side effects are the flu-like symptoms of fever, headache, myalgia. Serious hypersensitivity reactions have been reported.

**Interactions:** Interferon  $\gamma_{1b}$  impairs the hepatic metabolism of drugs metabolized by the cytochrome P450 system. The effects of alcohol are potentiated.

<i>Combination</i>	<i>Interaction</i>
<b>Antibiotics and antimalarials/oral live attenuated typhoid vaccine (8, 9)</b>	Oral typhoid vaccine is taken by mouth in an enteric coated capsule, one capsule being taken on alternate days for three doses. Protection may persist for up to three years. The vaccine is inactivated by concomitant administration of antibiotics or sulphonamides and mefloquine.
<b>Azathioprine/vaccines (10)</b>	The immunosuppressive activity of azathioprine could result in atypical and life-threatening infections in response to live vaccines. Killed vaccines are likely to be ineffective when given to patients on azathioprine. Hepatitis B vaccine being a case in point.
<b>Chloroquine/Rabies vaccine BP (11–12)</b>	Studies have shown that concomitant administration of chloroquine reduces the antibody response to this vaccine with human diploid cell rabies vaccine.
<b>Cyclosporin/vaccines (13–20)</b>	With killed vaccines there is reduced efficacy of the vaccine due to immunosuppression. With live vaccines there is a significant risk of severe infection. Prospective cyclosporin therapy warrants assessment of each patient's immune protection against infectious diseases preventable with vaccines or toxoids. Vaccines and toxoids require T-helper cells to exert their protective effect, and the action of cyclosporin is to suppress the action of T-helper cells. In general it appears that in patients on cyclosporin existing

<i>Combination</i>	<i>Interaction</i>
<b>Cyclosporin/vaccines cont.</b>	immune responsiveness is retained but the ability to evoke new immune responses is impaired.
<b>Insulin/interferon (49–52)</b>	A 66-year-old man with maturity onset diabetes developed a rapidly reversible increase in insulin requirement while receiving interferon $\alpha_{2a}$ for hepatitis C. The patient's diabetes had been controlled on 62 units of insulin (Mixtard) for 3 years. After 3 months treatment with interferon his insulin requirement had risen to 118 units of insulin per day. Interferon was discontinued and within 8 days his insulin requirement fell to 28 units per day (49). Impaired glucose tolerance has been shown in healthy subjects during interferon therapy (50) and in a non-diabetic patients treated with interferon for hepatitis (51, 52).
<b>Phenytoin/influenza vaccine (21–25)</b>	Contradictory results have been reported for the effects of influenza vaccine on serum phenytoin concentrations. Jann and Fidone (21) reported a significant elevation in total phenytoin concentration following vaccination which was suggested to be due to interferon induction and concomitant inhibition of cytochrome P450. In contrast, other reports have suggested that any increase in serum phenytoin concentration was temporary and not significant overall (22), or even that there was a slight fall in serum phenytoin concentration (23).
	One study reported a significant increase in total phenytoin concentration 2 days after vaccination, followed by a return to previous values but this was accompanied by evidence of a gradual and prolonged fall in free phenytoin concentrations (24). The possibility of either phenytoin toxicity or loss of seizure control may exist in some epileptic patients given influenza vaccine during phenytoin therapy (25).
<b>Theophylline/BCG (1, 26)</b>	Transient inhibition of the hepatic metabolism, possibly secondary to interferon production resulting in increased theophylline serum half-life and

<i>Combination</i>	<i>Interaction</i>
<b>Theophylline/influenza vaccines (27–37)</b>	<p>concentration has been reported after BCG vaccine. There is a possibility of theophylline toxicity.</p>
	<p>Eleven children whose asthma had been controlled with a stable theophylline dose developed signs of theophylline toxicity on the same dose during an influenza B outbreak (27). All had clinical evidence of a febrile viral illness. Two children had seizures, eight had nausea and vomiting, and three had headaches. Theophylline clearance gradually returned to pre-illness levels over a period of 1–3 months (27). These cases supported the earlier contention that theophylline clearance was decreased during natural viral respiratory infections (28–30). Decreased elimination of theophylline also occurred after influenza immunization in patients and in volunteer subjects (29). In contrast, other studies have indicated that influenza immunization had no effect on theophylline levels in patients with chronic airway obstruction (31, 32). However, the original investigators have reiterated their previous conclusion that influenza vaccine <i>does</i> alter theophylline's metabolism and have suggested that the discrepancy in findings may be due to the use of different vaccines and that these may have different peak timing of their depressant effect on drug metabolism (33).</p>
	<p>Agents that induce interferon can inactivate hepatic cytochrome P450. Inasmuch as viruses are inducers of interferon, this synthesis may be the most likely mechanism of influenza virus and vaccine in altering theophylline pharmacokinetics (34). Support is given to this by the demonstration that influenza vaccination depresses aminopyrine metabolism in man (35).</p>
	<p>More recently a study in elderly subjects showed that clinically significant reactions to warfarin or theophylline were rare after influenza vaccinations and were no more frequent than in those not receiving vaccinations. Further, following influenza vaccination in 13 elderly individuals serum concentrations of</p>

*Combination**Interaction***Theophylline/influenza vaccines cont.**

theophylline showed no change. Others have found no effect of influenza vaccine on theophylline clearance in normal subjects nor in those with chronic obstructive airways disease.

It must also be appreciated that, in theophylline-treated patients, symptoms of vomiting, headaches or seizures during viral illness may be due to theophylline toxicity rather than to the virus. Such patients should have an immediate serum theophylline determination even if previous levels were in the therapeutic range (27).

In practice, clinically significant interactions have been shown to occur with influenza virus infections but not following vaccinations.

The *British National Formulary* remains cautious by stating “plasma-theophylline concentrations occasionally increased by influenza vaccine”. The Data sheets to none of the commercially available influenza vaccines refer to this interaction (36) and the reference to this in the data sheets of theophylline preparations is not universal (37).

**Warfarin/influenza vaccine (35, 38–45)**

There have been a few reports of increased prothrombin time and bleeding in warfarin-stabilized patients following influenza vaccination. Studies investigating this possible interaction have found only a small or inconsistent increase in warfarin activity (35, 38–41) or no effect (42–44). One study suggested that influenza vaccine decreases rather than increases the prothrombin time (45).

**Warfarin/interferon  $\alpha$  (9, 46–49)**

The half life of warfarin is increased due to inhibition of cytochrome P450.

The fact that the metabolism of a number of drugs is inhibited by vaccines and this is due to interferon is supported by the work of Adachi *et al.* (46). After giving interferon to a patient with chronic hepatitis C, who had been taking warfarin, these clinicians observed increased anticoagulation. There was an

*Combination**Interaction*

increased serum warfarin concentration which necessitated a reduction in warfarin dosage. Their patient, a 52-year-old woman with a history of post-transfusion chronic hepatitis C after heart surgery, had received warfarin postoperatively. Her maintenance dose alternated between 3.5 and 2.5 mg daily. Investigations on admission to hospital showed a prothrombin time of 16.7 s (international normalized ratio of 1.60), a Thrombotest result of 27%, and a serum warfarin concentration of  $\leq 0.8$  mg/ml. She started taking human lymphoblastoid interferon  $\alpha$  at a dose of 6.0 MU daily for 14 days and then three times a week. Although the results of other liver function tests did not change appreciably, prothrombin time increased to 20.4 s (internationalized ratio 1.99). Thrombotest results decreased to 17% and serum warfarin concentrations rose to 5.2 mg/ml. Warfarin dosage was reduced stepwise to 2.0 mg/day. Some weeks later anticoagulation and serum warfarin concentrations had returned to nearly their initial values.

The authors of this report have also had to decrease the dose of warfarin in four other patients, two taking interferon  $\beta$  and two taking interferon  $\alpha_{2\beta}$  concomitantly with warfarin. Interferon does not directly affect the coagulation system, but it is known to inhibit hepatic microsomal enzymes, (47, 48) thus the potentiation of warfarin's activity is likely to be the result of a decrease in its hepatic metabolism. The authors warned that the degree of anticoagulation should be carefully monitored when interferon is given to patients who are receiving warfarin.

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# **CHAPTER 11**

## **Drug Interactions with Agents used in Anaesthesia**

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## **11.1. DRUG INTERACTIONS WITH LOCAL ANAESTHETICS**

Local anaesthetics act by producing a reversible block to conduction along nerve fibres, the smaller and unmyelinated nerve fibres are more sensitive than larger heavily myelinated nerve fibres. Therefore, it is possible to produce a differential block so that smaller fibres carrying pain sensation are anaesthetized but sparing coarse touch and movement.

### **I. LOCAL ANAESTHETICS OF THE ESTER TYPE**

**Amethocaine hydrochloride:** an effective local anaesthetic for topical application. It is rapidly absorbed from mucous membranes. *It should never be applied to inflamed or traumatized areas. It should never be used for bronchoscopy or cystoscopy.*

**Benzocaine** is a local anaesthetic of low potency. It is an ingredient of many proprietary throat lozenges.

**Cocaine** readily penetrates mucous membranes and is an effective surface anaesthetic with an intense vasoconstrictor action. It has marked sympathomimetic activity as a result of its intense stimulant effect on the CNS. It is a drug of addiction.

**Procaine hydrochloride:** local anaesthesia by infiltration and regional routes.

### **II. LOCAL ANAESTHETICS OF THE AMIDE TYPE**

**Bupivacaine hydrochloride:** the great advantage of bupivacaine over other local anaesthetics is its duration of action of up to 8 hr. It has a slow onset of action, taking up to 30 min. It is useful in lumbar epidural blockade and is suitable for continuous epidural analgesia in labour. It is the drug of choice for spinal anesthesia. *It is contraindicated in intravenous regional anaesthesia (Bier's block).*

#### **Butanilicaine phosphate**

**Lignocaine hydrochloride:** lignocaine is the most widely used local anaesthetic. It acts more rapidly and is more stable than other local anaesthetics. It is effectively absorbed from mucous membranes, and can therefore be used in surface anaesthesia. Except for surface anaesthesia solutions should not exceed 1%.

Lignocaine is frequently used with adrenaline 1 in 200 000.

In addition to its local anaesthetic uses lignocaine has a role as an antiarrhythmic agent.

Lignocaine should be used with caution in patients with epilepsy, impaired cardiac conduction with bradycardia, or porphyria.

Lignocaine can be used for surface anaesthesia, infiltration, injection, nerve block and epidural and caudal block.

### **Mepivacaine hydrochloride**

**Prilocaine:** prilocaine is a local anaesthetic of low toxicity and is similar in its uses to lignocaine. If used in high doses methaemoglobinemia may occur. This can be treated with intravenous methylene blue 1% at a dose of 1 mg/kg (Griffin 1997).

Drug interactions with local anaesthetics have been generally confined to four main areas: interactions associated with high doses of noradrenaline, interactions with anticholinesterases; interactions with suxamethonium; and interactions with sulphonamides. The risk of such interactions occurring is greatest when the local anaesthetic is given by injection; however, topical or ophthalmic use could initiate such interactions if the local anaesthetic reaches appreciable levels in the plasma.

<i>Combination</i>	<i>Interaction</i>
<b>Noradrenaline/local anaesthetic (1, 2)</b> butanilcaine phosphate/noradrenaline procaine phosphate/ noradrenaline lignocaine/noradrenaline	Fifteen cases of hypertensive episodes, one fatal, have been reported (1) in which local anaesthetic preparations containing high doses of noradrenaline (1 in 25 000 = 0.00004 g/ml) were used in dental anaesthesia. Six of these patients had been concurrently receiving treatment with tricyclic antidepressants.  Avoid local anaesthetics with excessively high concentrations of adrenaline or noradrenaline. The use of local anaesthetic formulations containing either of these vasoconstrictor agents is best avoided in patients on tricyclic antidepressants.
<b>Local anaesthetic/adrenaline or noradrenaline/antidepressant (1, 2)</b> MAOIs tricyclics	Vasopressor drugs (adrenaline, noradrenaline) in local anaesthetic preparations may induce hypertensive episodes in patients being treated with MAOI or tricyclic antidepressants.  The use of local anaesthetic agents containing either of these vasoconstrictor agents is best avoided in patients on antidepressants, especially tricyclic compounds.

<i>Combination</i>	<i>Interaction</i>
<b>Lignocaine/ antiarrhythmic agents</b> e.g. procainamide (3) Lignocaine/nitrates and prenylamine lactate (4)	<p>Neurological side effects have been reported (hallucination and delirium) when these two agents were given concomitantly.</p> <p>Two elderly patients treated with sublingual nitrates and prenylamine for stable angina suffered several episodes of syncope. Both patients showed a prolonged QT interval with premature ventricular beats and <i>torsade de pointes</i> ventricular tachycardia. The male patient showed sinus rhythm while the female had sinus bradycardia. After bolus doses of lignocaine (male, 100 mg; female, 50 mg) both experienced AV block.</p> <p>Pacemakers were inserted 3–5 days after withdrawal of prenylamine; the QT interval returned to normal and ventricular arrhythmias ceased. In two other patients with prenylamine-induced tachycardia, lignocaine neither precipitated AV block nor stopped the arrhythmias which were treated by pacemaker overdrive suppression. AV block after i.v. lignocaine is rare but it is possible that prenylamine and lignocaine may interact to cause AV conduction delays.</p>
<b>Local anaesthetic/ antibacterials</b> <b>(sulphonamide)</b> (5) in particular: amethocaine (tetracaine) benzocaine butacaine procaine	<p>Local anaesthetics which are derivatives of <i>p</i>-aminobenzoic acid (e.g. amethocaine, benzocaine, butacaine, procaine) are hydrolyzed in the body to <i>p</i>-aminobenzoic acid and should therefore not be used in patients being treated with sulphonamides.</p> <p>Sulphonamides exert their antibacterial action by competitive inhibition of <i>p</i>-aminobenzoic acid in the micro-organism, thus their activity may be antagonized by metabolites of these local anaesthetics.</p>
<b>Lignocaine/β-blocking drugs</b> propranolol (6–9) metoprolol (7) nadolol (8)	<p>Significant increases in plasma lignocaine concentrations have occurred (6–9) during concomitant therapy with β-blockers such as propanolol (6–9), metoprolol (7) or nadolol (8), owing to a reduction in the clearance of lignocaine from plasma. A review (10) of the available data suggests that the hepatic metabolism of lignocaine may be reduced as a result of a fall in hepatic blood flow associated with reduced cardiac output or it may be caused by a direct inhibition of hepatic microsomal enzymes. One study</p>

<i>Combination</i>	<i>Interaction</i>
<b>Lignocaine/<math>\beta</math>-blocking drugs cont.</b>	has suggested that the reduction in clearance with propranolol is mainly by direct inhibition of metabolism rather than by lowering of hepatic blood flow (10).
<b>Procaine/ecothiopate (11)</b>	The prolonged ophthalmic use of eclothiopate causes a reduced plasma pseudocholinesterase level, which results in reduced hydrolysis of procaine. This effect is potentially hazardous since it is known that patients with familial pseudocholinesterase deficiency have developed severe reactions, including unconsciousness and cardiovascular collapse, following the injection of procaine.
<b>Local anaesthetics/ <math>H_2</math>-receptor antagonists</b> cimetidine, ranitidine (12–17)	Studies of the effect of $H_2$ -receptor antagonists on the pharmacokinetics of bupivacaine have yielded variable results. While one group of investigators found that pretreatment with cimetidine decreases the clearance of bupivacaine (12), others have failed to find any significant effect (13, 14). Similarly, pretreatment with ranitidine has either increased plasma concentrations of bupivacaine (15) or had no significant effect (14). Cimetidine (300 mg quid for 1 day) given to six normal subjects reduced the systemic clearance of lignocaine (lidocaine) (1 mg/kg by 10 min i.v. infusion) from 766 to 47 ml/min; the apparent volume of distribution at steady state and the degree of plasma protein binding of lignocaine were also decreased. Five of the 6 subjects noted lignocaine toxicity during the cimetidine infusion when peak lignocaine concentration was raised by a mean of 50% (16). The mechanism of this interaction appears to be multifactorial, involving both altered distribution and clearance; these are likely to be due to cimetidine's known inhibition of oxidative pathways of biotransformation causing impaired metabolism of lignocaine and an induced decrease in liver blood flow via its vasoconstrictor effects on splanchnic circulation.  Side effects should be anticipated when i.v. lignocaine is given to patients also receiving cimetidine. The total dose of lignocaine should be infused slowly or given by

<i>Combination</i>	<i>Interaction</i>
	repeated small doses. Another report (8) cautions against routine administration of cimetidine to patients receiving lignocaine unless serum lignocaine levels are monitored or the dose of lignocaine is adjusted to counterbalance the enhanced and potentially toxic effects.
<b>Lignocaine/diuretics (18)</b>	The effect of lignocaine as an anti-arrhythmic agent is antagonized by hypokalaemia associated with acetazolamide, loop diuretics and thiazides.
<b>Lignocaine/plastics containers (19)</b>	The lignocaine content of buffered cardioplegic solutions has been reported to decrease when stored in polyvinylchloride containers at ambient temperature but not when stored at 4°C (19). This loss appeared to result from pH-dependent sorption of lignocaine onto the plastics material and did not occur when lignocaine solutions were stored in glass bottles.
<b>Lignocaine/smoking (20, 21)</b>	Smokers had a significantly lower plasma free fraction of lignocaine than non-smokers (mean: 0.258 vs. 0.307). This 19% increase in protein binding of lignocaine in smokers may be due to their higher concentrations of $\alpha_1$ -acid glycoprotein (20). Another study showed that the systemic bioavailability of lignocaine was decreased secondary to a marked increase in clearance after oral administration, reflecting an induction of drug-metabolizing activity (21).
<b>Local anaesthetic/suxamethonium Lignocaine/suxamethonium (22)</b>	Intravenous lignocaine has been shown to enhance the neuromuscular blocking action of suxamethonium. This interaction is thought to be due to lignocaine displacing suxamethonium from plasma protein binding sites. In addition lignocaine has anticholinesterase activity.
<b>Procaine/suxamethonium (22)</b>	Intravenous procaine has been shown to enhance the neuromuscular blocking action of suxamethonium. The mechanism of this interaction is two-fold; first, procaine displaces suxamethonium from plasma

*Combination**Interaction*

<b>Procaine/suxamethonium cont.</b>	proteins; secondly, since procaine and suxamethonium are both metabolized by plasma pseudocholinesterase, large doses of procaine competitively inhibit the metabolism of suxamethonium. In addition procaine has anticholinesterase activity.
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**INTERACTIONS WITH LOCAL ANAESTHETIC AGENTS *IN VITRO***

Drug interactions with local anaesthetic agents *in vitro* due to mixing of injectable formulations prior to administration can cause particular problems and are therefore dealt with separately.

*Combination**Interaction*

<b>Lignocaine/other drugs in solution (23–26)</b>	<p>Lignocaine hydrochloride is incompatible with the following drugs in solution causing precipitation of the other drug:</p> <ul style="list-style-type: none"> <li>ampicillin sodium (occasional depending on pH and vehicle) (23)</li> <li>amphotericin (24)</li> <li>cephazolin sodium (25)</li> <li>methohexitone sodium (26)</li> <li>phenytoin sodium (27)</li> <li>sulphadiazine sodium (26)</li> </ul> <p>Avoid these combinations; precipitation may not be immediately apparent and may develop slowly.</p>
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**Procaine/other drugs in  
solution (28–29)**

Procaine solutions are reported to be incompatible with aminophylline, barbiturates, magnesium sulphate, phenytoin sodium, sodium bicarbonate and amphotericin. Solutions should be protected from light (28).

Degradation of procaine solutions containing magnesium, sodium, potassium and calcium salts was found to be temperature dependent. When stored at 6°C the shelf-life of the solution was 5 weeks and this was increased to 9 weeks when the storage temperature was –10°C (29).

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## **11.2. SKELETAL MUSCLE RELAXANTS**

### **I. NEUROMUSCULAR BLOCKING DRUGS**

Muscle relaxants used in anaesthesia are also known as neuromuscular blocking drugs or myoneural blocking drugs. By specific neuromuscular blockade they enable lighter levels of anaesthesia to be employed with adequate relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and thus facilitate the passage of a tracheal tube. Their action differs from muscle relaxants acting on the brain or spinal cord which are used in musculoskeletal disorders.

*Patients who have received a neuromuscular blocking agent should always have artificial ventilation until the agent has been inactivated or antagonized.*

#### **1. Non-depolarizing (Curare-like) Agents**

Drugs of this group are competitive muscle relaxants and cause blockade by competing with acetylcholine at the receptor site of the neuromuscular junction. These agents produce neuromuscular blockade ranging from 15 min to 3 hr depending upon the agent selected.

Depolarizing neuromuscular blocking agents should be avoided in patients with myasthenia gravis.

The action of this group of agents can be reversed with variable sensitivity by neostigmine. When neostigmine is used to reverse neuromuscular block, atropine or glycopyrronium should be given before or with the neostigmine to avoid bradycardia, excessive salivation and other muscarinic effects of the neostigmine.

<i>Drug</i>	<i>Therapeutic effect</i>
<b>Alcuronium chloride (4)</b>	Elimination half-life of 3 hr.
	The majority (80–85%) of the drug is eliminated by the kidneys.
	Does not have ganglion blocking or histamine releasing or vagolytic effects.
	Neuromuscular block reversed by neostigmine.

<i>Drug</i>	<i>Therapeutic effect</i>
<b>Atracurium besylate</b> (12)	<p>Duration of action 15–35 mins.</p> <p>Histamine release may occur.</p> <p>Atracurium is without vagolytic or sympatholytic effects.</p> <p>Degradation is non-enzymic Hofmann elimination.</p> <p>Action reversed by neostigmine.</p> <p>Non-cumulative on repeated dosing.</p>
<b>Fazadinium bromide</b>	No longer available.
<b>Gallamine triethiodide</b> (3)	<p>Has more rapid onset and recovery than tubocurarine or pancuronium.</p> <p>Causes undesirable tachycardia by vagolytic action.</p> <p>It should be avoided in patients with severe renal disease.</p>
<b>Mivacurium</b> (6)	<p>Duration of action about 15 min.</p> <p>Histamine release can be pronounced.</p> <p>No significant vagolytic effects.</p> <p>Prolonged muscle paralysis in patients with atypical or low plasma pseudocholinesterase.</p>
<b>Pancuronium bromide</b> (5)	<p>Duration of action 45–60 min, but may be prolonged in the elderly.</p> <p>Prolongation of effect is seen in patients with renal failure.</p> <p>Does not cause ganglionic blockade or significant changes in cardiac output.</p>

<i>Drug</i>	<i>Therapeutic effect</i>
	Neuromuscular blockade can be reversed by neostigmine, together with atropine as an anticholinergic agent.
	Causes a reduction in the partial thromboplastin time and the prothrombin time as does tubocurarine.
<b>Tubocurarine chloride (1)</b>	<p>Starts to act between 3–5 min and neuromuscular block lasts for about 30 min.</p> <p>May cause erythematous rash on neck and chest due to histamine release.</p> <p>Onset of neuromuscular block maybe associated with hypotension, this is usually transient, but may be significant in poor risk patients.</p>
<b>Vecuronium (7)</b>	<p>Duration of action 20–30 min.</p> <p>Large doses may be cumulative.</p> <p>Does not cause histamine release, sympathetic blockage or have vagolytic effects.</p>
<i>Atracurium and vecuronium are generally regarded as the agents of choice. Atracurium because of its non-enzymic elimination, and vecuronium because it has by far the lowest propensity to cause side effects.</i>	
<i>Combination</i>	<i>Interaction</i>
<b>Amphotericin B/ non-depolarizing neuromuscular blockers (17–20)</b>	The hypokalaemia which may occur following amphotericin therapy enhances the effect of non-depolarizing muscle relaxants.
<b>Anaesthetic agents/ non-depolarizing neuromuscular blockers (1–9)</b>	Alcuronium, atracurium, gallamine, mivacurium, pancuronium, tubocurarine and vecuronium, have all been reported to have their action prolonged by the following general anaesthetic agents ether, cyclopropane, halothane, ketamine, methoxyflurane, enflurane, isoflurane, thiopentone and etomidate.

<i>Combination</i>	<i>Interaction</i>
<b>Antibiotics/ Non-depolarizing neuromuscular blockers</b> (1-7, 10-17)	Alcuronium, atracurium, gallamine, mivacurium, pancuronium, tubocurarine and vecuronium, have all been reported to have their action prolonged by clindamycin, colistin, kanamycin, neomycin, polymyxins, streptomycin, tetracyclines, tobramycin, framycetin, lincomycin, amikacin, gentamicin and other aminoglycoside antibiotics.
<b>Antidepressants/non- depolarizing neuromuscular blockers</b> (5)	The data sheet on pancuronium warns that MAOI can increase the neuromuscular blocking effect.
<b>Azathioprine/non- depolarizing neuromuscular blocker</b> (3, 18)	Azathioprine has been reported to reverse or decrease neuromuscular blockade by gallamine and other competitive muscle relaxants. Azathioprine probably inhibits phosphodiesterase activity at the motor nerve terminal resulting in increased release of acetylcholine.
<b>Calcium channel blockers/non- depolarizing neuromuscular blockers</b> (19, 20)	Nifedipine and verapamil may interfere with the release of acetylcholine and enhance the neuromuscular blocking effects of this class of neuromuscular blocking drugs. Potentiation of neuromuscular blockade has been reported and the block may be resistant to reversal with neostigmine; edrophonium may be required.
<b>Cardiac anti-arrhythmic agent/non-depolarizing neuromuscular blocker</b> (3, 11, 21, 23)	Quinidine administration to patients recovering from the effects of tubocurarine leads to recurarization and apnoea. Quinidine potentiates both depolarizing and non-depolarizing (curare-like) muscle relaxants.
	Avoid use of quinidine immediately pre- and postoperatively, since it can lead to recurarization after surgery.
<b>Cholinergic agents/non- depolarizing neuromuscular blockers</b> (19, 24)	Demecarium and echothiopate eye drops, neostigmine and pyridostigmine antagonize the effect of non-depolarizing muscle relaxants; conversely they enhance the effect of suxamethonium.

<i>Combination</i>	<i>Interaction</i>
<b>Diazepam/ non-depolarizing neuromuscular blockers (25–28)</b>	There are conflicting reports of the effect of diazepam on neuromuscular blocking agents; potentiation (25) or antagonism (25) of neuromuscular blocking agents and a lack of interaction has been reported (26–28).
<b>Diuretics/ non-depolarizing neuromuscular blockers Thiazides (29, 30)</b>	Thiazide diuretics increase the responsiveness to tubocurarine and gallamine, an effect that appears to be related to thiazide-induced K <sup>+</sup> deficiency.  Avoid K <sup>+</sup> depletion prior to elective surgery and, if possible, withhold the administration of the diuretic.
<b>Frusemide (31–33)</b>	Frusemide may potentiate the effect of tubocurarine and other non-depolarizing muscle relaxants in renal failure by depleting serum K <sup>+</sup> . But antagonism of tubocurarine by frusemide has also occurred (33).  It is recommended that oral frusemide be discontinued for 1 week, and parenteral frusemide for 2 days prior to elective surgery.
<b>Haemostatic/ non-depolarizing neuromuscular blocker (34)</b>	Aprotinin, a polypeptide derived from bovine lung tissue, has been implicated in causing apnoea in patients who had recently received suxamethonium or tubocurarine. The mechanism is unknown.  Avoid the use of aprotinin in patients who have received skeletal muscle relaxants during the previous 2 or 3 days.
<b>Imidazoles/ non-depolarizing neuromuscular blockers (5)</b>	The data sheet on pancuronium draws attention to the fact that the neuromuscular blocking effect may be enhanced by imidazoles and metronidazole.
<b>Lithium/ non-depolarizing neuromuscular blocker (2, 35)</b>	Lithium has been reported to potentiate the neuromuscular blocking effects of atracurium and pancuronium.

<i>Combination</i>	<i>Interaction</i>
<b>Drugs with local anaesthetic properties/ non-depolarizing neuromuscular blocker</b> (1)	Drugs with local anaesthetic properties including quinidine, $\beta$ -adrenergic blocking agents, phenytoin, and penicillamine have been reported to increase the effect of alcuronium.
<b>Magnesium salts/ non-depolarizing neuromuscular blocker</b> (36)	Parenteral magnesium enhances the effect of non-depolarizing neuromuscular blockers such as tubocurarine.
<b>Narcotic analgesics/ non-depolarizing neuromuscular blocker</b> (4)	Narcotic analgesics depress respiratory function and have an adverse effect on recovery of spontaneous respiration after anaesthesia where neuromuscular blockers have been used.

## 2. Depolarizing Muscle Relaxants

### Suxamethonium Bromide

Suxamethonium is the only commonly used agent in this group. With a 5-min duration of action it is ideal for the passage of a tracheal tube, but may be used in repeated dosage for longer procedures.

It acts by mimicking acetylcholine at the neuromuscular junction, but disengagement from the receptor site is slower than for acetylcholine; depolarization is therefore prolonged and neuromuscular blockade results.

Suxamethonium should always be given after induction of anaesthesia since depolarization of the muscles causes fasciculation or even a painful twitching.

Recovery from suxamethonium block is spontaneous, but unlike non-depolarizing neuromuscular blockers it cannot be reversed by neostigmine.

Suxamethonium is contraindicated in severe liver disease, and in burns patients.

Premedication with atropine is desirable.

Prolonged muscle paralysis may occur in patients with atypical or low plasma cholinesterase enzymes.

When repeated doses of suxamethonium have been used, dual block may occur. This is caused by a non-depolarizing block following the recovery from the depolarizing block. Dual block is diagnosed by giving a short-acting anticholinesterase such as edrophonium; if an improvement occurs this is diagnostic of a secondary non-depolarizing block and neostigmine should be given. Artificial ventilation should be continued until full muscle function is restored.

Post-operative pain and stiffness may occur after administration of depolarizing neuromuscular blocking agents.

<i>Combination</i>	<i>Interaction</i>
<b>Anticholinesterase/ suxamethonium</b> ecothiopate (37–42)	Prolonged use of ecothiopate eye drops in the treatment of glaucoma causes diminished serum cholinesterase levels. Thus prolonged apnoea and death have been reported with the administration of suxamethonium to patients with ecothiopate-induced depression of serum pseudocholinesterase.
<b>Antineoplastic agents/suxamethonium</b> (19, 43–45)	Cyclophosphamide, thiotepa, mustine and tretamine lower the serum pseudocholinesterase level possibly by alkylation of the enzyme and may give rise to prolonged apnoea if suxamethonium or other depolarizing neuromuscular blocking drugs are given.
	Check level of serum pseudocholinesterase in patients on such antineoplastic treatment; if levels are low, avoid the use of suxamethonium or other depolarizing neuromuscular blocking drug. If suxamethonium is necessary in such cases, use with extreme caution.
<b>Digitalis glycosides/ suxamethonium</b> (19, 46–48)	Suxamethonium appears to potentiate the cardiac effects of digitalis glycosides with respect to both conduction and ventricular irritability. Cardiac arrhythmias have occurred when suxamethonium has been administered to digitalized patients.
	Suxamethonium should not be used in digitalized patients unless absolutely necessary; neuromuscular blocking agents other than suxamethonium should be used.
<b>Histamine H<sub>2</sub> antagonists/ suxamethonium</b> (49–51)	There are conflicting reports on the effect of cimetidine on the neuromuscular blocking activity of suxamethonium: prolonged paralysis (49) and lack of interaction (50) have been reported. Famotidine and ranitidine have been reported not to interact with suxamethonium (51).
<b>Lithium/suxamethonium</b> (51)	Prolonged neuromuscular block has been reported following re-use of muscle relaxants in patients receiving lithium.

<i>Combination</i>	<i>Interaction</i>
<b>Metoclopramide/ suxamethonium (50, 52)</b>	Dose-dependent prolongation of suxamethonium-induced neuromuscular block has been reported in patients given metoclopramide. The potent inhibitory effect of metoclopramide on pseudocholinesterase may account for this interaction.
<b>Monoamine oxidase inhibitors (MAOI)/ suxamethonium (53)</b>	Phenelzine has been reported to cause a reduction in the level of plasma pseudocholinesterase. Prolonged apnoea in a patient on phenelzine has been reported after suxamethonium administration. There is no evidence at present that other MAOIs affect pseudocholinesterase.
	Caution should be exercised in administering suxamethonium (or other depolarizing muscle relaxant) to patients on phenelzine or other antidepressant of the MAOI type.

## II. AGENTS PRODUCING MUSCLE RELAXATION BY MECHANISMS OTHER THAN AT THE NEUROMUSCULAR JUNCTION

**Baclofen**

**Carisoprodol**

**Chlorphenesin carbamate**

**Chlorzoxazone**

**Cyclobenzaprine hydrochloride**

**Dantrolene sodium**

**Mephenesin and mephenesin carbamate**

These drugs are used in the treatment of muscle spasms; they diminish skeletal muscle tone and involuntary movement by a selective action on the CNS. Baclofen has been reported to have a predominantly spinal action and dantrolene is thought to have a direct action on muscle fibres of this grouping.

**Baclofen** is an antispastic agent acting at the spinal level. It is a  $\gamma$ -aminobutyric acid derivative. Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating GABA receptors. Neuromuscular transmission is unaffected by baclofen (54).

**Dantrolene** produces relaxation of contracted skeletal muscle by affecting the contractile response at a site beyond the myoneural junction. It is thought to produce

a dissociation of excitation/contraction coupling, probably by interfering with the release of calcium from the sarcoplasmic reticulum.

The use of dantrolene with hepatotoxic agents should be avoided. There is some evidence that hepatic injury is more likely in patients using concomitant oestrogen (presumably in the form of the contraceptive pill or in hormone replacement therapy, HRT) (55).

**Diazepam** and **quinine** also have a role in the treatment of muscle spasm and night cramps.

<i>Combination</i>	<i>Interaction</i>
<b>ACE inhibitors/baclofen</b> (19)	Enhanced hypotensive effect, hypotension is a common side-effect of baclofen.
<b>Alcohol/baclofen</b> (19, 24)	Enhanced sedative effect.
<b>Antidepressants/baclofen</b> (56–58)	Enhanced muscle relaxant effect. Nortriptyline and imipramine, separately, apparently potentiated the antispastic effect of baclofen in one patient. Prior treatment for 18 months with baclofen produced good relief of spasticity and left the patient with sufficient muscle tone to stand. However, 50 mg nortriptyline daily at bed time after 6 days caused increased weakness of the legs and he was unable to stand. Muscle tone returned after withdrawal of nortriptyline. Two weeks later imipramine 75 mg daily caused the same loss of muscle tone. This also abated within 2 days of withdrawal of the tricyclic. The mechanism of this interaction is uncertain although a number of possibilities have been suggested including a simple additive effect, an unmasking of pre-existing paresis as spasticity is diminished, displacement of baclofen from protein binding sites (this is unlikely since baclofen is not highly protein bound, whilst tricyclics are), or a pharmacodynamic interaction affecting neurotransmitters.

<i>Combination</i>	<i>Interaction</i>
<b>Antihypertensives/baclofen (19)</b>	Enhanced hypotensive effect.
<b>Lithium/baclofen (19, 24, 54)</b>	Lithium enhances the muscle relaxant effect of baclofen. Baclofen possibly enhances lithium-associated hyperkinesis.
<b>Levodopa + carbidopa/baclofen (54)</b>	There have been reports of mental confusion, hallucinations and agitation in patients receiving this combination of muscle relaxant and anti-parkinson therapy.
<b>Non-steroidal anti-inflammatory agents/baclofen (54)</b>	NSAIDS which produce renal damage including ibuprofen reduce baclofen excretion leading to toxicity.

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# CHAPTER 12

## Drug Interactions with Herbal Remedies

### INTRODUCTION

The use of natural (herbal) and other non-orthodox medicines is a persistent aspect of present-day health care and Europeans alone are thought to spend the equivalent of US \$500–600 millions/year on natural remedies and food supplements. Many consumers believe that naturalness is a guarantee of harmlessness and have no qualms in taking traditional herbal medicines as well as their own prescribed conventional medicines. In the United Kingdom, and elsewhere in Europe, many immigrant races have their own traditional medicine practices, which they frequently combine with orthodox medical care. Generally too little is known about the consequences of such combinations although the clinical reports of interactions that infrequently appear in the medical and pharmaceutical press suggest that many more interactions may be occurring that are not realized as such and are not reported in the literature.

Although herbal medicines are by far the largest component of non-orthodox remedies they do not have exclusive claims; it must be made clear that there are various types of other alternative treatments ranging from preparations of animal origin, to minerals, vitamins and amino acids. The following table is restricted to interactions with herbal medicines, interactions between minerals, vitamins and orthodox medicines have been reviewed in Chapter 15 (Nutrient–drug interactions) and also by other reviewers (1, 2).

It must be appreciated that the quality control over most herbal remedies, which are not officially registered as medicines, is often poor and more likely to be non-existent, and that most herbal preparations are not standardized for potency in biological test systems. As a consequence their potency may vary considerably from sample to sample. Furthermore they may be contaminated or adulterated with undeclared pesticides, toxic metals, botanicals, animal substances and/or orthodox

drugs which may lead to additional and unexpected adverse drug reactions and interactions (3–6).

<i>Combination</i>	<i>Interaction</i>
<b><i>Banisteriopsis/Psychotria leaves</i></b>	In South America a hallucinogenic drink called 'ayahuasca' is prepared from <i>Banisteriopsis</i> vines and <i>Psychotria</i> leaves. The former yields β-carotene alkaloids, but these are only hallucinogenic in high doses. The <i>Banisteriopsis</i> alkaloids are potent reversible MAOIs and selectively inhibit MAO-A. The addition of <i>Psychotria</i> leaves provides the alkaloid dimethyltryptamine which is hallucinogenic in low parenteral doses. The oral dimethyltryptamine would be inactivated by MAO-A but the presence of the <i>Banisteriopsis</i> β-carbolines in the drink prevents this degeneration (7, 8).
<b><i>Berberine/tetracycline</i></b>	This alkaloid is derived from the roots and bark of the plant <i>Berberis aristata</i> ; extracts of the plant have been used as antidiarrhoeal medication in Ayurvedic medicine in India and in the traditional medicine of China for the past 3000 years. A Burmese study on the clinical effects of berberine alone in watery diarrhoea, namely the reputed antisecretory and vibriostatic effect, showed that it did not benefit the duration of diarrhoea, the frequency of stools and fluid requirements for dehydration, nor did it produce a notable antisecretory effect. Clinically, patients with cholera given tetracycline plus berberine were more ill, suffered longer from diarrhoea and required greater volumes of intravenous fluid than did those given tetracycline alone (9).
<b><i>Betel nut (<i>Areca catechu</i>)/neuroleptics</i></b>	Two chronic schizophrenic patients who were maintained on depot neuroleptics developed serious extrapyramidal symptoms after a period of heavy betel nut chewing. The mechanism was suggested as antagonism of the neuroleptics by the active alkaloid ingredient of the betel nut (arecoline) (10).
<b><i>Anti-asthma drugs</i></b>	Betel nut chewing has been included among the factors that dispose to asthma severity and its unsatisfactory control by orthodox medicines in Asians residing in the

<i>Combination</i>	<i>Interaction</i>
	UK. It is suggested that arecoline, or another alkaloid in betel nut, for example guvacoline, may have a cholinergic bronchoconstrictor effect (11).
<b>Caffeine containing herbs/4-quinolones and fluoroquinolones</b>	The hepatic metabolism of caffeine is inhibited, its elimination half-life increased and its clearance decreased by certain antibacterial 4-quinolones and fluoroquinolones (ciprofloxacin, enoxacin, pipemidic acid and temafloxacin) (12–15). Users of caffeine-containing beverages and herbals should be advised that they have an increased risk of adverse effects (e.g. tremor, tachycardia, insomnia, CNS excitation) when they take such quinolines. The most important herbal remedies which contain substantial amounts of caffeine are derived from <i>Cola</i> , <i>Ilex</i> and <i>Paullinia</i> species (16).
<b>Cola nut/antipyrine</b>	An extensive study of factors affecting antipyrine in West African villagers showed that cola nut consumption inhibited antipyrine metabolism and prolonged its half-life by 3.5 hr. It was suggested that unidentified constituents of cola nuts competed with antipyrine for oxidation by the microsomal enzyme system (17). However, other work in Caucasian males failed to show any effect on antipyrine disposition, Genetic factors may therefore be of importance (18).
<b><i>Coprinus atramentarius/</i> alcohol</b>	The ink cap fungus is a component of some health foods. It contains bis(diethylthiocarbamoyl) disulphide, which is disulfiram, the active component of Antabuse. Ink cap reacts with small amounts of ingested alcohol to give unpleasant symptoms of systemic reactions (hypotension, nausea, sweating, facial flushing, throbbing headache, tachycardia, accelerated and deepened respiration and giddiness) (19, 20).
<b>Dietary fibres bran/digoxin</b>	Digoxin bioavailability is decreased by almost 20% when given with a high-fibre meal (21, 22).
<b>Bran/iron</b>	The bioavailability of dietary iron is reduced by bran (23).

<i>Combination</i>	<i>Interaction</i>
<b>Bran plus psyllium biscuits/riboflavine</b>	Absorption of riboflavine is reduced by 6.4% (24).
<b>Ispaghula husk/lithium salts</b>	Blood lithium concentration in a psychiatric patient treated with lithium salts fell to below acceptable levels when ispaghula husk (one teaspoonful in water twice daily) was taken (25).
<b>Pectin or bran/lovastin</b>	Concomitant fibre intake may decrease the absorption of the lipid-lowering agent lovastin. Patients showed greatly increased low-density lipoprotein cholesterol levels when these agents were introduced into a lipid-lowering diet plus lovastin; levels normalized when the fibres were stopped (26).
<b>High-fibre diet/tricyclic anti-depressants</b>	Excessive dietary fibre may reduce the efficacy of tricyclic antidepressants. Three patients with recurrent major depression became refractory to therapy after ingesting a high-fibre diet. Serum antidepressant levels were lower than those previously achieved (27).
<b><i>Eucalyptus</i> species</b>	A number of studies have demonstrated the eucalyptus leaves, its oil and active principle, eucalyptol, can induce microsomal enzyme activity in both <i>in vitro</i> and <i>in vivo</i> tests (28, 29). However, there have not been any recorded interactions between eucalyptus and orthodox drugs at the clinical level. Eucalyptus oil is a significantly toxic substance; poisoning affects the CNS (loss of consciousness, hypoventilation and convulsions), the gastrointestinal system (abdominal pain, vomiting and diarrhoea) and the respiratory system (pneumonitis and bronchospasm). The oil is readily available in Australian households and ingestion by young children is not uncommon (30).
<b>Garlic (<i>Allium sativum</i>)/anticoagulants</b>	Since garlic can reduce human platelet aggregation <i>in vitro</i> (31) it is difficult to exclude the possibility of untoward effects in patients taking anticoagulants. Two cases have been reported of increased international normalized ratios in patients previously stabilized on warfarin; the altered anticoagulation picture was

<i>Combination</i>	<i>Interaction</i>
	<p>attributed to the ingestion of garlic products (pearls or garlic tablets). Their clotting times were roughly doubled (32).</p> <p>However, an earlier review of the literature failed to disclose reports of an interaction between warfarin and garlic or any firm data on prolongation of prothrombin times by garlic (33). Nonetheless, other authors have warned that drugs, such as agents in garlic, which cause alterations in platelet function, may potentiate warfarin's action even though the prothrombin time remains unchanged (34). The present situation about this possible interaction is unclear.</p>
<b>Ginseng (<i>Panax ginseng</i>)/phenelzine</b>	<p>The concurrent use of ginseng and the MAOI phenelzine has been associated with adverse effects in two patients (35, 36). However, commercial ginseng preparations are not always derived from <i>Panax ginseng</i> and it is difficult to incriminate this official source plant in the interaction.</p>
<b>Digoxin</b>	<p>Serum digoxin levels were raised (from 0.9 and 2.2 mmol/l to 5.2 mmol/l) by ingestion of ginseng in a patient who had been maintained well on digoxin for 10 years. When the patient's digoxin dose was decreased and finally discontinued after 10 days, the serum digoxin levels remained high for a further 2 weeks. Once ginseng was stopped, serum levels of digoxin returned to normal when digoxin treatment was re-introduced. Rechallenge with ginseng resulted again in elevation of serum digoxin levels. Ginseng contains eleutherosides, which are chemically related to cardiac glycosides, and it was suggested that some component of the ginseng may have been converted to digoxin. However, since the patient remained asymptomatic during the interaction, it was suggested that the serum assay for digoxin had detected a compound in ginseng that gave a false reading (37).</p>
<b>Grapefruit juice/Ca antagonists, cyclosporin, caffeine, coumarin-yielding herbs</b>	<p>Grapefruit juice (but not other citrus juices) greatly augments the bioavailability of the antihypertensive calcium antagonists, felodipine nifedipine, nitrendipine and nisoldipine (38–42), the bioavailability of</p>

<i>Combination</i>	<i>Interaction</i>
<b>Grapefruit juice/Ca antagonists cont.</b>	cyclosporin (43, 44) and has similar results on the clearance of caffeine (46). It also inhibits the 7-hydroxylation of coumarins (47), this implies that grapefruit juice may interfere with the pharmacokinetics of coumarin-yielding medicinal herbs such as: <i>Melilotus officinalis</i> (sweet clover), <i>Asperula odorata</i> (sweet woodruff), <i>Dipteryx odorata</i> (tonka bean and <i>Anthoxanthum odoratum</i> (sweet vernal grass) (48–50).
<b>Terfenadine</b>	Taking the antihistaminic, terfenadine, with a large glass of fresh grapefruit juice markedly increased the area under the plasma level/time curve (AUC) in six subjects who were previously shown to be poor metabolizers of terfenadine. Levels increased up to five times with the greatest effect around 4–5 hr after the dose (51–53). This interaction is currently being investigated by the UK Medicines Control Agency as possible interaction between the juice and oestrogens (54).
<b>Oestrogens</b>	A similar interaction has been reported between grapefruit juice and oral but not intravenous midazolam, nifedipine and cyclosporin, which suggested that the site of the flavonoid effect was the gastrointestinal tract. A further study has shown that grapefruit juice delayed absorption of the anti-arrhythmic agent, quinidine, in healthy subjects and that it inhibited the metabolism of quinidine to 3-hydroxyquinidine and delayed the time to reach maximum plasma concentration (53).
<b>Midazolam</b>	
<b>Quinidine</b>	
<b>Guar gum/ glibenclamide, metformin, phenoxyethyl- penicillin</b>	The absorption of concomitantly administered drugs may be affected. The absorption of glibenclamide (55), metformin (56), and phenoxyethylpenicillin (57) may be significantly reduced.
<b>Kampo medicines/ prednisolone</b>	Oriental Kampo medicines often contain glycyrrhizin, and these have been reported to influence prednisolone pharmacokinetics. Three Kampo remedies which also contained Saiko ( <i>Bupleuri radix</i> ) and were commonly administered with prednisolone in

<i>Combination</i>	<i>Interaction</i>
	<p>the treatment of asthma, nephrotic syndrome and collagen disease, had a variable and different effect on prednisolone pharmacokinetics in healthy subjects. One of the three remedies had a steroid-sparing effect due to decreased <math>11\beta</math>-hydroxysteroid dehydrogenase (<math>11\beta</math>-HSD) activity. The other two increased or did not change the activity of this enzyme. Interestingly, the authors attributed the enzyme inhibitory effect not to glycyrrhizin, which was present in the three Kampos, but to magnolol which was only present in the Kampo with a positive effect on prednisolone metabolism (58). Follow-up work confirmed that magnolol might contribute to the inhibitory effects of magnolol on prednisolone metabolism through inhibition of <math>11\beta</math>-HSD (59).</p>
<b>Karela (<i>Momordica charantia</i>)/chlorpropamide</b>	<p>It has long been established that oral preparations of this oriental folk remedy have hypoglycaemic activity in non-insulin-dependent diabetic patients (60). Interference with conventional treatment of diabetes by diet and chlorpropamide has been observed (61). It has also been reported that a subcutaneously injected principle obtained from the fruit may have a hypoglycaemic effect in insulin-dependent diabetics (62).</p>
<b>Kyushin/digoxin</b>	<p>A traditional component of this Chinese medicine is the venom of the Chinese toad (<i>Bufo bufo gargarizans</i>). The venom contains bufalin and cinobufaginal which are chemically similar to digoxin. The preparation may therefore interfere with digoxin immunoassays, the constituents can react with digoxin antibodies and create a false impression of high plasma digoxin levels (63–67).</p>
<b>Liquorice/anti-hypertensives</b>	<p>Liquorice (root or extract) may be ingested in confectionery, soft drinks, medicines or chewing tobacco. It has mineralocorticoid effects due to the saponin glycoside, glycyrrhizin, which results in <math>\text{Na}^+</math> and water retention and the development of hypokalaemia (68, 69), oedema and hypertension (70, 71). These effects are thought to be due to inhibition</p>

<i>Combination</i>	<i>Interaction</i>
<b>Liquorice/ anti-hypertensives cont.</b>	<p>of <math>11\beta</math>-hydroxysteroid dehydrogenase by glycyrrhetic acid (a metabolite produced by the hydrolysis of glycyrrhizin) resulting in increased concentrations of cortisol in the body (69–73). The control of hypertension may be difficult.</p> <p>Hypokalaemia and <math>\text{Na}^+</math> caused by liquorice in a laxative preparation was associated with flaccid quadriplegia in a 70-year-old woman (74). The diagnosis was confirmed by challenge with controlled administration of the laxative. The safe upper limit of glycyrrhizin is often considered to be in the range of 150–200 mg/day, as liquorice intoxication is usually associated with daily amounts exceeding these levels.</p>
<b>Prednisolone</b>	<p>An intravenous infusion of the active principle, glycyrrhizin, increased the total and free plasma concentration of prednisolone and influenced the pharmacokinetics of prednisolone in man (75). The AUC of prednisolone was significantly increased, the total plasma clearance was significantly reduced and the mean residence time was significantly prolonged. There was, however, no evident change in the volume of distribution. It has been suggested that this combination would be advantageous in the treatment of rheumatoid conditions. The basis of the interaction has been suggested as an inhibition of the metabolism of the steroid by microsomal enzymes. There is experimental evidence that glycyrrhizin and glycyrrhetic acid can inhibit <math>5\alpha</math>, <math>5\beta</math> and <math>11\beta</math>-dehydrogenase reductase (76, 77).</p>
<b><i>Picrorhiza kurroa</i>/ methoxsalen</b>	<p>The rhizomes of this plant species is thought to potentiate the photochemotherapeutic effects of methoxsalen in human patients with vitiligo (78).</p>
<b>Piperine/various drugs e.g. phenytoin propranolol rifampicin sulphadiazine tetracycline theophylline</b>	<p>Several studies show that piperine, a major alkaloid of <i>Piper longum</i> and <i>P. nigrum</i>, both of which occur in Ayurvedic formulations, can enhance the bioavailability of orthodox drugs such as: phenytoin, propranolol, rifampicin, sulphadiazine, tetracycline and theophylline. Among the suggested mechanisms are promotion of gastrointestinal absorption, inhibition of drug metabolism and a combination of the two (79–84).</p>

<i>Combination</i>	<i>Interaction</i>
<b><i>Psilocybe semilanceata/ alcohol, psychoactive drugs</i></b>	Forty-nine patients were admitted to a Glasgow hospital after the deliberate ingestion of 'magic mushrooms'. This gill fungus contains psychoactive substances such as psilocybin and psilocin, which can act on indoles in the CNS to produce symptoms that can mimic acute toxicity and schizophrenic states (85). The effect is potentiated by alcohol and there is obviously a serious risk of interaction with other psychoactive drugs that may be taken concomitantly.
<b><i>Shankhapusphi/ phenytoin</i></b>	Two epileptic patients taking phenytoin experienced unexpected loss of seizure control and a reduction in plasma phenytoin levels when they took this herbal preparation, which is a non-alcoholic syrup prepared from six herbs: <i>Centella asiatica</i> , <i>Convolvulus pluricaulis</i> , <i>Nardostachys jatamansi</i> , <i>Nepeta elliptica</i> , <i>Nepeta hindostana</i> and <i>Onosma bracteatum</i> . A follow-up study in animals confirmed these effects. Paradoxically Shankhapusphi itself showed antiepileptic activity (electroshock seizure prevention) when compared with placebo (86).
<b><i>Sparteine-containing herbs/ quinidine, haloperidol moclobemide tricyclic and SSRIs antidepressants</i></b>	Sparteine is a quinolizidine alkaloid from <i>Cytisus coparius</i> which was recently found in a herbal slimming remedy in the UK. Substantial doses of this preparation in slow metabolizers could be expected to be associated with many adverse reactions including circulatory collapse (87). Quinidine is a potent inhibitor of the oxidative metabolism of sparteine (88) and a similar effect has been observed with haloperidol (89) and moclobemide (90). In addition, several <i>in vitro</i> studies have shown that several antidepressants (tricyclic or SSRIs) inhibited human liver microsomal P4502D6 (CYP2D6) activity which resulted in a reduced oxidative conversion of sparteine to dehydrosparteine (91).
<b><i>Teas/iron</i></b>	Ordinary tea is sometimes reputed to affect oral iron absorption (92) and some workers have assessed the effect of other herbal teas. Freshly prepared rooibos tea ( <i>Aspalathus linearis</i> ) did not affect iron absorption in contrast to ordinary tea (93); anise, mint, caraway,

<i>Combination</i>	<i>Interaction</i>
<b>Teas/iron</b> <i>cont.</i>	cumin, tilia and liquorice promoted the absorption of iron (92). Other workers dispute that ordinary tea affects the absorption of pharmacological doses of oral iron preparations (94).
<b><i>Teucrium chamaedrys/ clofibrate</i></b>	Hepatotoxicity has been reported with this herbal preparation (95); toxicity is attenuated by inducers of microsomal epoxide hydrolase (such as clofibrate).
<b>Vitamin K-containing herbs/anticoagulants</b>	Herbal preparations and food supplements containing appreciable quantities of vitamin K can reduce the effects of oral anticoagulants (96). Cases of impaired anticoagulation have been recorded after concomitant intake of 'Gon', a non-orthodox remedy containing vitamin K <sub>1</sub> , and also after excessive amounts of green vegetables (96–101).
<b>Yohimbine/tricyclic anti-depressants chlorpromazine amylobarbital reserpine clonidine</b>	This toxic alkaloid from <i>Pausinystalia yohimbine</i> causes hypertension in patients taking tricyclic antidepressants (102). Its toxicity can be enhanced by chlorpromazine, and attenuated by amylobarbital or reserpine (103). Yohimbine may be portrayed in health foods as a peripheral vasodilator which can potentiate other blood pressure-lowering agents. In reality, however, the $\alpha$ -adrenoreceptor antagonistic properties of the alkaloid will reverse the effects of clonidine and similar antihypertensives (104).

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# **CHAPTER 13**

## **Drug Interactions with Medicinal Plastics**

### **INTRODUCTION**

It has been increasingly evident in recent years that the rapid change from glass containers to the almost universal use of plastics as infusion containers, as well as for the administration systems, has generated some unforeseen adverse effects (1). The following are the polymer compounds and other materials (medicinal plastics) that are widely used in plastics pharmaceutical packaging, syringes, filters and intravenous administration equipment:

**Cellulose esters (acetate, nitrate, propionate)**

**Ethylvinyl acetate**

**Methacrylate butadiene styrene**

**Nylon**

**Polyacrylonitrile**

**Polybutadiene**

**Polycarbonate**

**Polyethylene**

**Polyolefin**

**Polypropylene**

**Polystyrene**

**Polyurethane**

**Polyvinyl chloride**

**Rubber**

**Silicone**

**Teflon**

## ABSORPTION

Plastics materials used in medicine and pharmacy may interact with medicinal substances principally by absorption (sorption), adsorption and permeation. Of these mechanisms, absorption into a plastics material is probably the most important mechanism underlying interactions. For example the sorption of drugs to intravenous fluid containers, delivery sets, syringes, filters and other plastics apparatus has been well publicized and it is apparent that materials made from polyvinylchloride (PVC) are the major offenders in this respect. Interactions with other plastics are rare. Additives present in the plastics materials include plasticizers added to reduce brittleness, ultraviolet ray absorbers to prevent degradation by light, and antioxidants and lubricants which are sometimes needed for satisfactory processing. Such plasticizers may provide an appropriate hydrophobic environment for drug migration. Monomer residues and additives can leach out from the finished plastics materials and have been responsible for contamination of container contents (1-6).

Current information suggests that the following drug substances may exhibit clinically significant sorption to plastics materials: amiodarone, some benzodiazepines including diazepam and lorazepam, chlormethiazole, glyceryl trinitrate (nitroglycerin), hydralazine hydrochloride, insulin, isosorbide dinitrate, lignocaine, phenothiazines, thiopentone sodium, vitamin A acetate and warfarin sodium.

## ADSORPTION

The classic example of a drug binding to surfaces is insulin, which has been found to adsorb equally to glass, PVC or polyethylene. Adsorption may be reduced by other solutes which compete for the same binding sites (e.g. other proteins like albumin or gelatin). These facts distinguish adsorption from absorption (sorption). The major clinically important effect is that, as the adsorption process occurs so rapidly, doses administered initially are much reduced but, as surfaces become saturated, the dose of drug received by the patient increases rapidly. Losses can be minimized by using the high concentration – small container approach to drug delivery (e.g. a syringe with a high concentration of drug in solution).

## LEACHING

Leaching is the migration of substances from the container or packaging materials into the medicine. A number of drugs, or components of their formulation, cause the leaching of the plasticizer diethylhexyl phthalate (DEHP) from PVC bags into intravenous solutions. These drugs include the antineoplastics teniposide, paclitaxel (Taxol) and its semisynthetic analogue docetaxel (Taxotere), cyclosporin and miconazole (7, 8).

With teniposide, large amounts of DEHP were extracted from PVC infusion bags and to minimize patient exposure to this substance teniposide solutions should be stored in glass or a polyolefin container and delivered through polyethylene-lined i.v. administrations sets (9).

Paclitaxel and docetaxel are formulated for injection in dehydrated alcohol and polyoxyethylated castor oil, the latter being known to leach DEHP from PVC containers and administration sets (10,11). No DEHP was detected when solutions were stored in glass or polyolefin containers and infused through polyethylene-lined administration sets (10). After storage for 19 hr in 1% methanolic aqueous solution, the concentration of Taxol (paclitaxel) declined to about 40% in glass vials, 67% in polypropylene tubes, and 55% in siliconized polypropylene tubes. When stored in polystyrene tissue culture plates the concentration decline to 73% after 24 hr; no concentration decline was observed in the presence of foetal bovine serum (12).

Cyclosporin and miconazole are also formulated with surfactants when used in injection solutions and these also leach DEHP from plastics bags and administration sets. To minimize patient exposure to DEHP these solutions should be infused immediately after their preparation in PVC bags (8).

## PERMEATION

Certain drugs not only absorb into plastics but permeate through the plastics matrix to be released from the outside surface. Loss of chlormethiazole from PVC sets and catheter-related thrombophlebitis during chlormethiazole administration through silicone catheters are probably due to this property (4). Nitrates are thought to behave in a similar fashion when in contact with PVC and this will greatly contribute to nitrate loss during parenteral administration (1).

In addition, some drugs have been shown to alter the physical characteristics of plastics materials, for example, the general anaesthetic gas, cyclopropane, is incompatible with flexible plastics or rubber tubing; methoxyflurane a volatile anaesthetic is significantly absorbed by the rubber in anaesthetic circuits and it partially solubilizes PVC plastics. Paraldehyde has long been known to have a solvent action on rubber, it also solubilizes polystyrene and styrene-acrylo-nitrile copolymer and therefore should not be injected with syringes made with these materials.

Glass is usually a satisfactory alternative for those drug substances that interact with plastics, however, there are exceptions. For example, chloroquine binds strongly onto soda glass (60–70% bound) and insulin is strongly absorbed by laboratory glassware and siliconized glassware (13,14).

## CONTACT LENSES

A number of drugs can enter into surface interactions with plastic contact lenses. A search of the literature has not shown any other examples of this interaction other than those included in the last edition of this volume. It would seem therefore that this type of interaction is not a major clinical problem although it is possible that new interactions have been experienced but not reported. In any event, the importance of such interactions has greatly diminished due to the development of single-use 'disposable' lenses.

## CONCLUSIONS

The following Table of Drug Interactions gives information on those interactions between drugs and plastics materials that have clinical significance. No drug should be added to any intravenous fluid unless it is known that the drug is stable in the fluid and that it does not interact with the materials of the container or administration equipment.

Most reports of interactions between drugs and plastics materials have originated from studies to determine the stability of drugs in plastics containers, syringes, plastics infusion bags, filters or giving sets. The number of such studies is legion and it would be impossible for any book of this size to cover even a small percentage of the number of reports that have appeared in the literature. We do not know of any specific book that lists these types of interaction and we would therefore direct any enquirer to the latest editions of the *ABPI Data Sheet Compendium*, *Martindale*, *The Extra Pharmacopoeia*, or the *British National Formulary* or other national reference sources.

<i>Combination</i>	<i>Interaction</i>
<b>Plastics/amiodarone</b>	This anti-arrhythmic agent is rapidly sorbed by PVC infusion bags (losses up to 60% after 5 days) and administration sets (losses up to 18% after 15 min). Losses were attributed to the presence of the plasticizer di-2-ethylhexylphthalate. There were no losses when stored in glass or rigid polyvinyl chloride bottles (15).
<b>Plastics/carbamazepine</b>	There is an apparent loss of carbamazepine during administration through nasogastric feeding tubes. Twelve methods of administering carbamazepine suspension (100 mg/5 ml) were tested; the methods differing with respect to tube size, presence and type of diluent, and type of flush solution. Significant loss of carbamazepine (up to 23.6%) was noted for four of the six methods in which undiluted suspension was administered. No significant loss of drug occurred for any of the methods involving the use of a diluent. These results indicated that undiluted suspensions adhere (sorb) to polyvinyl nasogastric feeding tubes (16). It is important to note that similar problems have arisen with the administration of phenytoin by this route (17). Carbamazepine suspensions should be mixed with an

<i>Combination</i>	<i>Interaction</i>
	equal volume of diluent before being administered through nasogastric feeding tubes.
<b>Plastics/chlormethiazole</b>	Several studies have demonstrated that chlormethiazole edisylate may permeate through or be sorbed onto plastics used in intravenous infusion bags or administration sets (4, 18–20). The drug may also react with and soften the plastics material (3, 4). The UK manufacturers recommend the use of a motor-driven glass syringe in preference to a plastics drip set in small children. If a plastics drip set is used in older patients it should be changed at least every 24 hr. In all cases Teflon intravenous cannulas should be used. Chlormethiazole penetrates the walls of silicone tubing, such as those found in silastic catheters, and has led to thrombophlebitis along the length of a vein (5).
<b>Plastics/chloroquine</b>	Various studies, using low concentrations of chloroquine phosphate or sulphate have shown that chloroquine exhibits pH-dependent binding to several materials used in medical equipment and membrane filters including soda glass, and various plastics, such as cellulose acetate, cellulose propionate, methacrylate butadiene styrene, polypropylene, polyvinyl chloride, ethylvinyl acetate and polyethylene (21–23). Although this effect may not be of relevance at doses used clinically (24), it is considered critical that laboratory workers undertaking assays and sensitivity testing should recognize that significant reductions in concentrations can occur when chloroquine solutions are prepared or stored in equipment made from these materials (22, 23). As the effect of borosilicate glass or polystyrene on chloroquine sorption appears to be minimal, it has been suggested that they be used in such procedures (22, 23). Similar sorption has been noted during membrane filtration of other antimalarial agents including amodiaquine hydrochloride, mefloquine hydrochloride and quinine sulphate (21). Both chloroquine and quinine sulphate should be

<i>Combination</i>	<i>Interaction</i>
<b>Plastics/chloroquine cont.</b>	protected from light as photodegradation will also cause losses of drug from solution. Mefloquine hydrochloride has been reported to undergo photolytic degradation in water (25).
<b>Plastics/cyclosporin</b>	It is common practice to measure serum levels of cyclosporin to avoid over or under dosage. This has led to the development of a number of therapeutic monitoring techniques, e.g. radioimmunoassay, and HPLC. However, a number of these techniques gave erroneous cyclosporin levels due to analytical problems (26). The use of an inappropriate pipette for manipulating cyclosporin standards led to low measured concentrations of the drug. This was due to the pipette having a plastics tip (rather than a glass tip) to which cyclosporin adsorbed. Sorption was attributed to the lipophilic nature of cyclosporin and it is now recommended that serum level monitoring techniques should use glass apparatus where possible (27).
<b>Plastics/diazepam and lorazepam</b>	Substantial adsorption of diazepam onto some plastics materials may cause problems when administering the drug by continuous intravenous infusion. More than 50% of diazepam in solution may be adsorbed onto the walls of PVC infusion bags and their use should therefore be avoided. Administration sets should contain the minimum amount of PVC tubing and should not contain a cellulose propionate volume-control chamber. Suitable materials for infusion containers, syringes, and administration sets when administering diazepam include glass, polyolefin, polypropylene and polyethylene (24, 28–32). Lorazepam should not be administered in sodium chloride or dextrose injections in PVC bags; the concentration of lorazepam dropped below 90% of the original concentration when stored in PVC bags. It was stable for up to 24 hr when stored in glass bottles (33). Rapid and unacceptable loss (up to 29% in 24 hr) of lorazepam in PVC bags occurred due to sorption. Lorazepam loss was greatly reduced in polyolefin bags (5% loss in 24 hr at room temperature) (34). Further studies confirmed significant losses due to probable

*Combination**Interaction*

sorption to PVC bags when admixed in both 5% dextrose and saline solutions (35, 36).

**Plastics/glyceryl trinitrate**

The loss of glyceryl trinitrate (nitroglycerin) from solution by adsorption or absorption into some plastics materials used in intravenous infusion equipment (37, 38) and inline filters (39, 40) has been recognized for some years, although adsorption does not appear to occur to any great extent with polyolefin (41) or polyethylene (24, 42, 43). Polypropylene or glass syringes have been recommended (44). The use of PVC containers, filters, tubing and administration sets should be avoided (45).

One study, however, showed that patients who received i.v. nitroglycerin through a PVC administration set had the same clinical response as patients given the drug through a polyethylene set (46).

Some commercial formulations of glyceryl trinitrate for intravenous use may contain substantial quantities of alcohol in the solvent, and there have been several reports of alcohol intoxication occurring during high-dose glyceryl trinitrate infusion (47-49).

A blood alcohol concentration of 2.67 mg/ml was reported in a patient who required glyceryl trinitrate 2 mg/min. PVC tubing has been used for the infusion and the authors suggested that adsorption of glyceryl trinitrate on to the tubing had increased the dose requirements and thus the amount of alcohol given (49).

**Plastics/insulin**

Insulin, in common with many polypeptides, may be strongly sorbed to glassware, to polyethylene and polyvinyl chloride (13, 50-52).

When insulin solutions are placed into plastics containers the fraction of insulin bound to the plastic has been reported to range from 5 to 80% (53). The sorption of insulin to plastics materials can present potential problems during the intraperitoneal administration of insulin to patients being treated with ambulatory peritoneal dialysis; as much as 65% of insulin added to 2 l of dialysis solution was retained by

*Combination**Interaction***Plastics/insulin cont.**

sorption to the material of the plastics container (54). The binding of insulin onto glass and plastics used in administration sets has been decreased by the addition of albumin or polygeline to insulin solutions. Some workers consider this to be unnecessary since in their experience insulin binding is not a major problem (55, 56). Running approximately 10 ml of the insulin solution through the intravenous tubing before beginning the infusion has been suggested by some (57).

Storage of biosynthetic insulin in polypropylene and propylene-ethylene copolymer syringes for 28 days did not cause significant insulin loss, but prefilled syringes should be refrigerated (58).

**Plastics/isosorbide dinitrate**

The loss of isosorbide dinitrate from solution during infusion was found to be 30% with PVC infusion sets, but negligible when polyolefin or glass delivery sets were used (59). An earlier study reported up to 50% loss when stored in plastic infusion bags or in the isolated burettes, but not during storage in glass containers over a period of 200 hr (60). Another study reported a 23% decrease after 24 hr storage at 21°C in PVC containers; most of the loss occurred within the first 6 hr. There was no loss of potency when isosorbide was stored under similar conditions in glass bottles or polyethylene, nylon, and polypropylene laminated bags (24).

**Heparin**

Continuously infused isosorbide dinitrate with heparin both have a compatibility problem with PVC tubing. Isosorbide dinitrate is rapidly fixed on PVC and then released; it is released earlier when it is administered with heparin in the tube. Some heparin is lost in the PVC tubing; this loss is relatively stable with time and is independent of the type of infusion solvent or whether heparin is used by itself or in combination with isosorbide dinitrate (61).

**Plastics/paraldehyde**

Paraldehyde has a solvent action upon rubber, polystyrene and styrene-acrylonitrile copolymer, and should not be administered in plastic syringes made with these materials (62). On re-evaluation of the

<i>Combination</i>	<i>Interaction</i>
	compatibility of paraldehyde with plastic syringes and needle hubs, it was recommended that, if possible, all-glass syringes be used for the injection of paraldehyde or for the measurement of oral doses. Needles with plastic hubs could be used. The use of polypropylene syringes with rubber-tipped plastic plungers (Plastipak), or glass syringes with natural rubber-tipped plastic plungers (Glaspak) was acceptable only for the immediate administration or measurement of paraldehyde doses (63).
<b>Plastics/propofol</b>	The anaesthetic propofol is formulated as an oil in water emulsion for injection. There was a significant decrease in concentration when the diluted emulsion was administered via PVC i.v. tubing; this was dependent upon the flow rate of the infusion (64). One manufacturer has suggested that it should be administered into a running i.v. infusion through a Y-site close to the injection site.
<b>Plastics/quinidine gluconate</b>	Spectrophotometric analysis of quinidine gluconate solutions in 5% dextrose injection administered via PVC administration sets revealed a 5–7% reduction in absorbance, associated with the loss of quinidine from the infusion bags and a further 34–38% reduction in absorbance attributable to quinidine absorption by the PVC tubing. However, with a glass syringe attached to a short PVC tube and a winged i.v. catheter the loss was reduced to less than 3%. Apart from absorbance, leaching of diethylhexyl phthalate could lead to apparent quinidine loss due to changes in UV light absorbance (64).
<b>Plastics/vitamin A</b>	A number of studies have shown that vitamin A binds to plastics, especially PVC, and losses can be as high as 80% (2, 5, 66). It is now clear that sorption to bags and administration sets depends on the ester used. While the acetate ester is strongly bound, the palmitate shows little or no tendency to bind to PVC. Vitamin A (both acetate and palmitate) is sensitive to light, and light-induced degradation, especially when passing through administration sets, may account for

*Combination**Interaction***Plastics/vitamin A cont.**

some of the reported high losses of vitamin A from solution (5). It must be accepted that vitamin A losses will occur with the acetate during parenteral nutrition, although not in the refrigerator if light protected. For example, in one study the amounts of vitamin A delivered to the patient from glass or PVC containers were 77 and 71%, respectively, when protected from light and 61 and 49% when exposed to light (67). The problem of sorption to PVC or other plastics can be solved by the use of the palmitate ester. This is more satisfactory than the empirical alternative of adding a generous excess of vitamin A acetate to the infusion fluid to allow for sorption losses. However, the use of the palmitate ester does not solve the problem of photodegradation of the vitamin.

Vitamin A tablets stored in PVC blister packs for 6 months showed degradation and loss of content (68).

**Plastics/various drugs in solution**

There have been some reports of studies directed specifically towards discovering plastics-drug interactions. In one study of 46 injectable drugs stored in PVC bags for periods up to 3 months, five drugs (chlormethiazole edisylate, diazepam, hydralazine hydrochloride, thiopental sodium and warfarin) were lost from solution due to substantial sorption after 1 week (3). In a follow-up study, 45 drugs were added to i.v. infusion fluids and drug loss was studied after simulated infusion via plastic infusion sets, with and without burette chambers and glass infusion bottles, via polyethylene and silastic tubing with glass syringes on an infusion pump, and via single-use all-plastic syringes. Chlormethiazole edisylate, chlorpromazine hydrochloride, diazepam, promethazine hydrochloride, thiopental sodium, thioridazine hydrochloride and trifluoperazine dihydrochloride were lost from solution during infusion through at least one of the systems (30). The loss of most drugs during infusion was slow, time-dependent and concentration independent, which indicated a diffusion-controlled sorption rather than a binding adsorptive process. Drug loss was lowest in short lengths of small diameter tubing with low

<i>Combination</i>	<i>Interaction</i>
	<p>permeability constants. None of the drugs was lost when stored in all-plastic, single-use syringes (30). A further study repeated this type of investigation and showed that up to 55% of diazepam, 51% of nitroglycerin, 24% of warfarin sodium, and 22% of isosorbide dinitrate was lost during 24 hr storage in PVC bags, but none lost potency when stored in glass bottle and Clear-Flex bags (polyethylene, Nylon and polypropylene laminate) (24).</p> <p>Other workers have dealt specifically with interactions between selected drugs and plastics syringes since it is common hospital practice to preload syringes with drugs and store them ready for use. Four drugs (dexamethasone sodium phosphate, diazepam, diatrizoate meglumine and nitroglycerin) were individually loaded into 3-ml syringes and stored at a range of temperatures for periods of 6 hr to 30 days. Drug concentrations were seen to change following storage, the greatest changes occurred with the highly lipophilic drugs dexamethasone and diazepam. In most instances loss of drug was most rapid at room temperature (69).</p>
<b>Plastic contact lenses/ various drugs</b>	Some drugs can enter into surface interactions with plastic contact lenses. For example, an orange colouration of lenses has been associated with the use of rifampicin (70), and brown adrenochrome pigmentation of hydrophilic lenses occurred with three elderly patients within 2 months of starting topical treatment with adrenaline hydrochloride or epinephryl borate (71); lens staining has also been reported with fluorescein (72). Other authors have reported opaque deposits in SeeQuence disposable contact lenses in three patients after treatment with topical ciprofloxacin and prednisolone acetate (73).
Contact lenses	Several papers have reviewed the use of contact lenses and medicaments that can affect them (74-78).
Intraocular lenses	Other work has investigated the <i>in vitro</i> washout kinetics of dexamethasone, gentamicin, norepinephrine and pilocarpine on intraocular lenses of different materials ranging from hydrogel lenses to

<i>Combination</i>	<i>Interaction</i>
Intraocular lenses <i>cont.</i>	polymethylmethacrylate, Acrysof and silicone lenses, Chiroflex and AMO SI-18NB. Maximum drug uptake would only provide one-tenth of the greatest aqueous humour concentrations that occurs after topical drug administration (79). Similar <i>in vivo</i> studies showed that hydrogel intraocular lens did not act as a significant depot for chloramphenicol and dexamethasone in the eye (80).
<b>Ramipril/ polyacrylonitrile dialysis membranes (81)</b>	Ramipril should not be used in patients using polyacrylonitrile (AN69) dialysis membranes or during low-density lipoprotein apheresis with dextran sulphate.

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# CHAPTER 14

## Drug Interactions with Alcohol

### INTRODUCTION

Patients taking medicines are commonly warned to avoid drinking alcohol but the advice is often imprecise, misleading or even unnecessary (1, 2). In this section we examine the interactions between medicines and alcohol and suggest ways of making the advice more helpful.

Usually the advice given is simply 'avoid alcoholic drink' (BNF). What patients need to know, however, is whether abstinence should be total, for how long any abstinence should apply and what the risks might be. The principle concerns are that drinking alcohol will reduce the efficacy of the medication or increase its unwanted effects. Many of the interactions arise because drugs and alcohol can interfere with each other's metabolism. Other interactions occur if their CNS depressant effects summate (2).

### METABOLISM OF ALCOHOL

Some 90–98% of ingested alcohol is oxidized to acetaldehyde in the liver mainly by the enzyme alcohol dehydrogenase. The acetaldehyde is converted by aldehyde dehydrogenase to acetyl-coenzyme A, which is then oxidized to CO<sub>2</sub> and water, or used in the synthesis of cholesterol and other tissue constituents. Alcohol may also be metabolized to acetylaldehyde by the liver microsomal mixed-function oxidases. The contribution of this pathway is usually small but it increases when the blood alcohol concentration is high. Age, gender and genetic factors influence rates of metabolism and affect the way individuals respond to alcohol (2).

Drugs that inhibit the oxidation of acetaldehyde can cause a systemic reaction if taken with alcohol (e.g. disulfiram). Other drugs also inhibit aldehyde dehydrogenase and cause acetaldehyde to accumulate in the blood (e.g. metronidazole, cepham-

andole), whilst chlorpropamide increases acetaldehyde levels and causes a facial flush in about one-third of patients if taken with alcohol. Flushing after alcohol has also been reported in patients taking procarbazine (3), oral ketoconazole (4) and, in one patient, griseofulvin (5). It is not known if these reactions are caused by inhibition of acetaldehyde metabolism. Verapamil delays the elimination of alcohol and prolongs alcohol intoxication (6).

### ACUTE OR CHRONIC ALCOHOL INTAKE

Alcohol may interfere with the effects of drugs metabolized by liver microsomal enzymes. The type of interaction depends on whether the alcohol intake is acute or chronic. Binge-drinking inhibits the metabolism of drugs by competing for microsomal enzymes. In contrast, regular consumption of large amounts of alcohol (more than 25 units per day) (7, 8) induces liver microsomal enzymes and so can increase the metabolism of co-consumed drugs. This may, however, be offset by alcohol-induced liver damage. Potentially important interactions can occur with drugs such as phenytoin, warfarin and tolbutamide in chronic heavy drinkers; serum levels of these drugs are reduced by one-third to one-half. Serum levels of drugs are unlikely to be affected by moderate or occasional drinking (9, 10).

In chronic heavy drinkers, alcohol may induce the enzymes that convert paracetamol to its hepatotoxic metabolite (*N*-acetyl-benzoquinoneimine). At the same time malnourishment may cause glutathione deficiency with impairment of the 'mopping-up' process for the hepatotoxin (11).

The CNS effects of alcohol may add to the CNS depressant effects of drugs such as sedatives, hypnotics, anxiolytics, opioid analgesics, antidepressants, antipsychotics, anti-epileptics and H<sub>1</sub>-antihistamines. The effect of the interaction on wakefulness, concentration and performance will depend on the dose of the drug and the pattern of alcohol intake. Patients should be warned of this and that the effects of alcohol may be exaggerated (2).

Alcohol, even in moderate amounts, may cause acute vasodilation, especially of skin blood vessels. Patients taking hypotensive agents such as ACE inhibitors, nitrates,  $\beta$ -blockers or  $\alpha_1$ -blockers may develop postural hypotension, with dizziness and fainting shortly after taking a drink. Conversely, regular intake of more than 4 units/day may raise blood pressure and is a risk factor for stroke (12).

### CONCLUSION

Alcohol interacts with many drugs, increasing or reducing the effect of some and itself being affected by others. Abstaining from alcohol altogether is usually unnecessary and may result in the patient becoming non-compliant. There are only a few instances in which women who drink up to 2–3 units/day, and men up to 3–4 units/day should abstain totally from drinking alcohol. For other drugs that interact, patients need to be advised of the likely effects if they drink whilst taking medic-

ation. For patients who are alcoholics, it may be necessary to adjust the dose of medication (2).

The Table of Drug Interactions in this section gives specific detail of the sequelae and management of interactions between alcohol and co-consumed medication.

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/analgesic acetaminophen (paracetamol)</b>	<p>Heavy drinkers have an increased risk of liver damage after moderate overdoses of paracetamol (11). Severe liver failure developed in three alcoholics after taking therapeutic doses of paracetamol; one died in hepatic coma (13).</p> <p>Patients should be warned of this effect (14). See introduction to this section for mechanism of induction and cause of toxicity.</p>
<b>Aspirin</b>	<p>Two subjects showed expected and moderate prolongation of bleeding time which peaked at 12 hr and returned to normal by 24 hr after aspirin (325 mg) ingestion. A second rise in bleeding time at 36 or 60 hr was associated with alcohol intake 4 hr earlier (15).</p> <p>Patients should be warned of this possibility; gastrointestinal irritation to aspirin may be worsened by alcohol intake. Advise no or low alcohol intake.</p>
<b>Dextropropoxyphene</b>	<p>There have been a disturbing number of deaths from either accidental or intentional overdosage. Overdosage is often complicated by patients also taking alcohol and using mixed preparations such as dextropropoxyphene with paracetamol or aspirin. Death has occurred rapidly (within an hour) and the quantity of dextropropoxyphene taken has often been small (16–24).</p>
<b>Alcohol/anticoagulant</b>	<p>Acute alcohol intake, even in moderate amounts, potentiates the action of coumarin anticoagulants (e.g. warfarin) by competitive inhibition of their hepatic enzyme metabolism. In alcoholics the half-life of warfarin is reduced due to alcohol induction of liver microsomal enzymes.</p> <p>In chronic heavy drinkers the half-life of warfarin is reduced (7), but patients with liver dysfunction who are well controlled on warfarin may become over anticoagulated after binge drinking (25).</p>

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/anticoagulant cont.</b>	The most critical factor is that the alcohol intake is relatively constant from day to day. In one study a daily intake of 7 units (3 at lunchtime and 4 with food in the evening) or less had no effect on warfarin levels or anticoagulant control (26). However, for practical purposes it may be best to advise patients to avoid alcohol.
<b>Alcohol/anticonvulsant</b>	In a double-blind, placebo-controlled study in 29 patients with epilepsy, moderate social drinking had no effect on seizure frequency, EEG activity or blood concentrations of carbamazepine, ethosuximide or phenytoin (24). Sodium valproate levels (which commonly fluctuate in individual patients) rose slightly. In chronic heavy drinkers (>30 units/day), serum levels of phenytoin are reduced by about one third (10). Serum levels of phenytoin are not affected by moderate or occasional drinking (29). Although there is no published evidence, carbamazepine is likely to be affected similarly (2).
<b>Alcohol/antidepressant MAOIs</b>	Hypertensive reactions may occur due to the tyramine content of some alcoholic drinks, notably beers and both red and white wines (27, 28). Recommend avoiding all alcoholic beverages including low-alcohol or alcohol-free beers; these beers are also rich in tyramine (27). There is no evidence of an interaction between alcohol and moclobemide, the reversible inhibitor of monoamine oxidase-A (29).
<b>Tricyclic (polycyclic) compounds</b>	Enhanced sedation, inhibition of intestinal movement, and fatty changes in the liver are consequences of this interaction. Ability to drive or operate machinery may be grossly impaired. Patients may show unusual and unexpected behavioural disorders, especially during the first few days of treatment (30–34). Advise low to no alcohol intake.
<b>Selective serotonin re-uptake inhibitors</b>	The effects of alcohol may be potentiated by these agents (35).

<i>Combination</i>	<i>Interaction</i>
<b>(SSRIs)</b>	SSRIs impair the ability to drive and operate machinery and these may be further impaired by the effects of alcohol.
<b>Alcohol/antidiabetic agent</b>	Large intakes of alcohol may cause severe hypoglycaemia (36–38). In general, diabetic patients do not need to abstain from alcohol completely but they should not exceed 3 units/day (men) or 2 units/day (women) (39). However, patients need to take account of the calorific value of alcohol, including any sugar-containing mixers, in the management of their diet (2).
<b>Biguanides (metformin) sulphonylureas</b>	<p>In patients on metformin, binge-drinking increases the risk of lactic acidosis (40–42). In alcoholics there is induction of hepatic microsomal enzymes and a reduced half-life of, for example, chlorpropamide and tolbutamide (7, 43).</p> <p>In heavy drinkers (30 units/day) blood levels of tolbutamide are roughly halved (7). Blood clearance of tolbutamide is unlikely to be affected in those who drink only a few times per week, or in ex-drinkers with advanced, but well-compensated cirrhosis of the liver (8).</p> <p>Chlorpropamide facial flush (CPAF) has been suggested as a marker for a special type of non-insulin-dependent diabetes and may be akin to metencephalin-induced flush. A central prostaglandin-dependent step in CPAF is proposed and blockade by aspirin is thought to be due to interference with prostaglandin synthesis (38, 44–53).</p> <p>Facial flushing occurred in two of 43 non-insulin-dependent diabetics treated with tolbutamide (54).</p>
<b>Alcohol/antihypertensives</b> <b>ACE inhibitors</b> <b><math>\beta</math>-blockers</b> <b>Ca<sup>+</sup>-channel blockers</b> <b>diuretics</b> <b>enzyme inhibitors</b>	Alcohol, even in moderate amounts, may cause acute vasodilation, especially of the skin blood vessels. Patients taking medication such as ACE inhibitors, nitrates, $\beta$ -blockers or $\alpha_1$ -blockers may develop postural hypotension, with dizziness and fainting, shortly after having a drink, particularly at the start of

<i>Combination</i>	<i>Interaction</i>
e.g. methyldopa nitrates, etc.	treatment (2). Conversely, regular intake of more than about 4 units/day probably raises blood pressure and is a risk factor for stroke (12).
<b>Alcohol/bromocriptine</b>	Reduced tolerance to bromocriptine (35). Alcohol-enhanced nausea and symptoms of bromocriptine toxicity were reported in two woman patients. Abstinence from alcohol reduced their severity and incidence and higher doses of bromocriptine could be tolerated (55). Alcohol intolerance was reported in five of 73 patients receiving bromocriptine for the treatment of acromegaly (56).
<b>Alcohol/cephalosporin</b>	A disulfiram-like reaction occurs with the parenteral cephalosporin, cephalexin, but not with other cephalosporins available in the UK. Patients given cephalexin should be advised to abstain from alcohol while receiving the drug and for 72 hr (or a week in patients with renal impairment) after stopping it (2).
<b>Alcohol/chlormethiazole</b>	Although chlormethiazole is a popular choice for the treatment of alcohol withdrawal symptoms, if it is given long-term, alcoholics readily transfer dependency to it, often while continuing to abuse alcohol. The outcome of such combined abuse is often severe self-poisoning with deep coma and potentially fatal respiratory depression (57). Five fatal cases of self-poisoning have been reported in chronic alcoholics being treated with chlormethiazole (58).
<b>Alcohol/cimetidine</b>	There is continuing dispute as to whether a significant interaction occurs with cimetidine. Although cimetidine inhibits alcohol dehydrogenase in the gastric mucosa the significance of this site for alcohol metabolism is uncertain (59). Studies have reported both significant increases in blood alcohol (60, 61) and a lack of such increases (62, 63). Current views appear to be that any interaction is unlikely to be clinically important (59, 64).

<i>Combination</i>	<i>Interaction</i>
<b>Alcohol/CNS depressants</b> e.g. benzodiazepines, barbiturates, sedative-hypnotics, anticholinergics, antihistamines, analgesics, antipsychotics, antidepressants, anticonvulsants, muscle relaxants	The CNS effects of alcohol may add to the CNS depressant effects of drugs such as hypnotics, anxiolytics, opioid analgesics, antidepressants, antipsychotics, anti-epileptics, and H <sub>1</sub> -antihistamines. It is difficult to predict if an interaction will occur that affects wakefulness and performance. The extent of the interaction will depend on the dose of the drug and the pattern of alcohol intake. Patients should be warned about any possible interaction due to alcohol intake and how it could affect them (e.g. drowsiness, poor concentration, reduced ability to perform certain tasks. They should be advised that the effects of alcohol may be exaggerated (2).
<b>Alcohol/disulfiram and disulfiram-like agents</b> e.g. metronidazole cephalosporin cephamandole	Disulfiram inhibits the oxidation of acetaldehyde; this reaction is the basis for the use of disulfiram in encouraging alcohol abstinence. The reaction which includes facial flushing, throbbing headache, hypotension, palpitations, tachycardia and nausea and vomiting starts 5–15 min after drinking alcohol and lasts several hours. It is rarely dangerous but collapse, cardiac arrhythmias and even death have occurred (65). In susceptible patients this reaction may be triggered by small amounts of alcohol in cough linctuses, some mouthwashes and food. Flushing may occur if alcohol-containing substances (e.g. aftershave lotions) are applied to the skin (66). Metronidazole, like disulfiram, inhibits aldehyde dehydrogenase and causes acetaldehyde accumulation in the body. The reaction is likely to be more severe the higher the dose of metronidazole and the amount of alcohol ingested. Interactions have occurred in women using vaginal metronidazole but are uncommon (67). Patients should not drink alcohol while taking metronidazole and for 48 hr after stopping it. The data sheet for tinidazole, a related drug, warns about the possibility of a disulfiram-like interaction although there are no published reports of such effects (2). A disulfiram-like reaction also occurs with the parenteral cephalosporin, cephemandole (68), but not with other cephalosporins available in the UK. Patients should abstain from alcohol while taking the antibiotic

Combination	Interaction
<b>Alcohol/disulfiram and disulfiram-like agents</b>	and for 72 hr (or 1 week in cases of renal impairment) after stopping it.
<i>cont.</i>	

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# CHAPTER 15

## Nutrient–Drug Interactions

### INTRODUCTION

Nutrient–drug interactions are not as often reported as drug–drug interactions but their potential frequency is far greater since food is by far the most common substance associated with the ingestion of oral doses of medicines (1–5).

Nutrients may affect the bioavailability and clinical efficacy of oral medication. On occasion, the interactions may indeed evoke toxicity as with hypertensive episodes following tyramine–monoamine oxidase inhibitor (MAOI) antidepressant interactions. Many medicines are linked with meals in dosing directions and interactions between them deserve much more emphasis and attention.

### ABSORPTION OF MEDICINES: PHYSIOLOGICAL MECHANISMS

Most oral drugs pass from the lumen of the gut across the epithelial lining into the adjacent splanchnic capillary network of the blood circulation. This is a passive process and food may interfere with drug absorption or elimination by altering splanchnic blood flow. The bulk-volume of the food can also have a pronounced effect. Other mechanisms of interaction include changes in gut motility, better drug absorption in the presence of a fatty meal, better drug dissolution and dispersion, decreased protein binding, acute changes in hepatic enzyme activity, and changes in gastric acidity. Such mechanisms have been recently reviewed by Welling (6).

Reduced or delayed absorption may be due to delayed gastric emptying or dilution of the drug in the gut contents (7). Gastric emptying times may be delayed by hot meals (8), high fat content (9) and high viscosity solutions (10). In general, fatty meals delay gastric emptying times to a greater extent than either protein-rich or carbohydrate-rich meals (9). Delayed absorption of drugs brought about by food

does not always imply that a lesser amount of drug is absorbed, but rather that the time for a drug to reach peak levels after a single dose is lengthened ((11)).

Vitamin and mineral supplements are a common combination and are readily obtained as non-prescription medicines. The possibility of their interaction with prescribed medicines may not be appreciated. It is the mineral component of the combination product, as well as the mineral content of antacids and some laxatives that is responsible for the majority of these interactions. It should not be forgotten that many foods are rich in minerals and these may also enter into interactions (e.g. with tetracyclines and dairy products), in addition branded breakfast cereals have added minerals and vitamins. A list showing the mineral content of common food-stuffs is given at the end of this chapter (*Table 6*), and in this respect it must be remembered that the portion of food normally consumed should be taken into account as well as its mineral content.

The following Tables of Drug Interactions are divided into two main parts; firstly, those nutrient-drug interactions causing reduced/delayed absorption or reduced bioavailability, and secondly those interactions causing increased absorption or bioavailability. These are based on a recent review by D'Arcy (12).

## PART 1: REDUCED OR DELAYED ABSORPTION AND REDUCED BIOAVAILABILITY

For convenience, drugs other than antimicrobial agents are listed in *Table 1* and antimicrobial agents in *Table 2*.

Drug names printed in bold face in the table are those which enter into well-

*Table 1.* DRUGS (OTHER THAN ANTIMICROBIAL AGENTS) WHOSE ABSORPTION FROM THE GUT MAY BE REDUCED (R) OR DELAYED (D), OR WHOSE THERAPEUTIC EFFECTS MAY BE ANTAGONIZED (A), OR WHOSE BIOAVAILABILITY MAY BE REDUCED (RB) BY THE PRESENCE OF FOOD OR METAL IONS (SPECIFIED)

acetaminophen (D) (13)
<b>alendroate sodium</b> (R) (14–16)
ambenonium chloride (R) (17)
aminohexane diphosphonate (AHDP, neridronic acid) (R) (18)
atenolol (R) (Al ions) (19)
<b>bisphosphonates</b> (R) (14–16, 20–26)
captopril (R) (27, 28)
carbidopa (R) (29)
chloroquine (R) (30, 31)
<b>digoxin</b> (D) (32–34)
<b>etidronate</b> (R) (20–23)
flecainide (R) (milk) (35)
<b>levodopa</b> (R) (iron salts) (29, 36) (food, amino acids) (37–40)
β-methyldigoxin (D) (32)
methyldopa (R) (41)
<b>nitrendipine</b> (R) (42–44)
pamidronate disodium (R) (22)
<b>penicillamine</b> (R) (food, iron, antacids) (45, 46) (RB) (47)
phenytoin (R) (antacids) (48, 49)
pyrimethamine (R) (30)
tiludronate (R) (30)
<b>warfarin</b> (A) (50–55)

Table 2. ANTIMICROBIAL AGENTS WHOSE ABSORPTION FROM THE GUT MAY BE REDUCED (R) OR DELAYED (D), OR WHOSE BIOAVAILABILITY MAY BE REDUCED (RB) BY THE PRESENCE OF FOOD OR METAL IONS (SPECIFIED)

---

amoxycillin (D, R) (56)
ampicillin (R) (56)
<b>azithromycin</b> (R) (57, 58)
benzylpenicillin G (R) (metal cations) (59)
cefaclor (D) (60)
cefixime (D) (60)
ceprozil (R) (61)
cephalexin (D) (60)
cephalosporins (D) (60–62)
cephradine (D) (60, 63)
cetibutene (R) (62)
chlortetracycline (R) (64)
ciprofloxacin (R, RB) (dairy products) (65) (antacids, Al, Ca, Fe, Mg salts) (66–72)
cloxacillin (R) (73)
demeclocycline (R) (food, milk, metal cations) (64, 74–77)
<b>didanosine</b> (RB) (78, 79)
<b>doxycycline</b> (R) (food, milk, metal cations) (64, 74–77)
erythromycin base or stearate (R) (depends on formulation) (59)
isoniazid (R, RB) (80)
lincomycin (R, D) (81)
methacycline HCl (R) (food, milk, metal cations) (64)
<b>minocycline</b> (R) (metal cations) (72, 82).
nafcillin sodium (R, D) (83).
norfloxacin (D) (84) (Fe, milk, yoghurt) (85, 86)
ofloxacin (D) (59)
oleandomycin (D) (59)
<b>oxytetracycline HCl</b> (R) (food, milk, metal cations) (64)
<b>quinolones</b> (D) (84, 87–94)
penicillins (most) (R) (post-prandial) (95–97)
rifampicin (RB) (98)
roxithromycin (R) (when taken after but not before meals) (99)
rufloxacin (R) (Al-Mg antacids) (100)
sodium fusidate (D) (101)
sulphonamides (D) (11, 102)
<b>tetracycline HCl</b> (R) (milk, dairy products, metal cations) (64, 82, 103)
<b>tetracyclines</b> (R) (59, 74–77)
<b>zidovudine</b> (D) (104, 105) (R) (106, 107)

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documented, clinically important interactions. The remaining drug entries are those whose interactions are likely to be clinically important although they lack good documentation. Interactions which are likely to be clinically irrelevant have been excluded from the list.

This table includes bisphosphonates used in the treatment of osteoporosis; Articles in the literature contain specific warnings about their interaction with vitamins or foods with a mineral supplement or content (1, 3, 14–16, 20–26). Material with a high calcium content, such as milk, may reduce the absorption of bisphosphonates. Vitamins with mineral supplements, calcium supplements, laxatives containing magnesium, or antacids containing calcium or aluminium, should not be taken within 2 hr of dosing with a bisphosphonate. The elderly osteoporotic woman may need special counselling to understand when to take calcium or iron

supplements, which are often recommended for the elderly. Such restrictions may be confusing to her unless they are explained.

Two AIDS medicines have been listed in *Table 2* and further detail is necessary in view of the importance of these treatments. Nutritional problems have been a part of the clinical aspects of AIDS from its earliest recognition. Wasting and diarrhoea will occur sooner or later and most patients with clinically advanced AIDS and opportunistic infections are anorexic and suffer from micronutrient deficiencies (108). AIDS patients tend to increase their intake of nutrients for which some data support a role in improving health, resistance to infections and, in some instances, inhibition of HIV replication *in vitro* (109–113). AIDS sufferers often consume many times the recommended daily allowance for minerals and vitamins (114).

With current knowledge, only two drugs used in AIDS and HIV infection seem to be affected by diet. First, oral absorption of zidovudine is reduced when the drug is taken with a high-fat content meal compared with fasting for at least 6 hr (104, 105). Other studies have reported significantly delayed and reduced absorption when the drug is taken with food (106, 107), although not with a protein-based meal. Thus, to achieve a high peak plasma concentration zidovudine should be taken on an empty stomach. The second drug, didanosine, which has activity against retroviruses, including HIV, is acid-labile and when given by mouth it should be taken under fasting conditions as food reduces its bioavailability (78, 79).

## PART 2: INCREASED DRUG ABSORPTION OR BIOAVAILABILITY

A variety of drugs (*Table 3*) and antimicrobials (*Table 4*) are better absorbed or have improved bioavailability if taken with food. Increased absorption has been attributed to a number of mechanisms including delayed stomach emptying which permits greater dissolution of the drug, improved dispersion, reduced protein binding and increased splanchnic blood flow (115).

Drug names printed in bold in these tables are those with well-documented evidence of clinically important nutrient–drug interactions. The remaining interactions are also clinically important, but there is less firm evidence of this.

There are a number of drugs mentioned in this table that enter into an interaction with grapefruit juice and potentiate their effects. This potentiation is thought to depend on the inhibitory effect of the flavonoids (e.g. naringin, quercetin) exclusive to grapefruit juice on the hepatic cytochrome P450 isoenzymes (CYP1A2, CYP3A4) which are responsible for the metabolism of these drugs (see review (118)).

## COMMENT

Special comment is necessary on two categories of drugs, firstly, the MAOI antidepressants and, secondly, on the variety of sustained-release formulations that are now available for a number of drugs.

**Table 3.** DRUGS (OTHER THAN ANTIMICROBIAL AGENTS) WHOSE ABSORPTION FROM THE GUT MAY BE ENHANCED (E) OR WHOSE BIOAVAILABILITY MAY BE ENHANCED (BE) BY THE PRESENCE OF FOOD OR METAL IONS (SPECIFIED)

aminopyrine (E) (107)
cyclosporin (BE) (grapefruit juice) (116–118)
danazol (BE) (119)
felodipine (BE) (grapefruit juice) (120)
fenretinide (BE) (121)
hydralazine (BE) (122, 123)
ibuprofen (E) (Mg ions) (124)
labetalol (BE) (125)
methoxsalen (E) (7)
<b>metoprolol</b> (BE) (food, AlOH <sub>3</sub> ) (126, 127)
midazolam (BE) (128)
nifedipine (BE) (grapefruit juice) (42, 120)
nisoldipine (BE) (grapefruit juice) (129)
nitrendipine (BE) (grapefruit juice) (43)
<b>propranolol</b> (BE) (126)
pseudoephedrine (E) (130)
spironolactone (E) (131)
terfenadine (E) (132, 133)
ticlopidine (E) (134)
tramadol (E) (135)
vinoxerine (BE) (high-fat meal) (136)
vinpocetine (BE) (137)
zalosprone (E) (138)

**Table 4.** ANTIMICROBIAL AGENTS WHOSE ABSORPTION FROM THE GUT MAY BE ENHANCED (E) BY FOOD AND/OR MINERAL SALTS

<b>cefuroxime axetil</b> (E) (139–144)
clofazimine (E) (145)
griseofulvin (E) (146–148)
itraconazole (E) (149, 150)
ketoconazole (E) (conflicting evidence) (151)
<b>nitrofurantion</b> (E) (152–154)

## MAOI ANTIDEPRESSANTS

The use of monoamine oxidase inhibitor antidepressants (MAOIs) has diminished over the years in favour of more recently introduced agents (e.g. tricyclics, tetracyclines and related compounds, and selective-serotonin re-uptake inhibitors (SSRIs)). However, cases of hypertensive episodes from interaction with tyramine or other pressor amine-containing foods and beverages still occur spasmodically (155, 156) and patients taking these drugs must be warned to avoid such foods and beverages. Furthermore, if their medication is changed from MAOIs they must allow a 14-day drug-free period before use of food or drugs known to cause reactions. A reversible selective MAO-A inhibitor, moclobemide, is suggested to have fewer systemic side effects and a reduced risk of dietary and drug interaction than irreversible MAOIs (157). *Table 5* lists some foods and beverages reported to be rich in tyramine content.

*Table 5. SOME FOODS AND BEVERAGES REPORTED TO BE RICH IN TYRAMINE CONTENT\**


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avocado pears
broad bean pods
beers, including low-alcohol beers
Bovril
canned figs
caviar
cheese (unprocessed, especially Cheddar and Gruyère)
Chianti wine, all other wines (red or white)
chocolate
game and game products
liver (especially chicken liver)
Martini
New Zealand prickly spinach ( <i>Tetragonia tetragonoides</i> )
pickled herring
yeast products (including Marmite)
yoghurt

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\*Source: Basu (7), Griffin *et al.* (158).

### SUSTAINED-RELEASE FORMULATIONS

Sustained- or controlled-release formulations may influence nutrient–drug interactions. Evidence from the literature is diffuse but there are reports which indicate that there could be a problem. For example, absorption of the  $\beta$ -blocker metoprolol has been shown to be significantly increased by food (126, 127). However, the drug in its controlled-release formulation of metoprolol succinate is affected far less by food than the conventional release formulation (159).

Divergent results have also been reported with different formulations of verapamil. There was a 30% reduced absorption and a 45% reduced peak serum level when the drug was taken as a sustained-release tablet with food (160). However, in other studies using a capsulated sustained-release formulation, plasma profiles were superimposable in the fed and fasting states (161, 162). In a further study, the drug was administered as extended-release pellets in the fasting state and with food; plasma verapamil profiles were the same for both treatments (163). An extensive review on drug–food interactions has been produced by Welling (6) which *inter alia* has covered food interactions with controlled-release preparations.

### MINERAL CONTENT OF FOODS

*Table 6* lists the mineral ion content (Ca, Cu, K, Mg, Na, Zn) of common foods. The table is a guide to assist practitioners in advising patients to avoid specific mineral-rich foods or alternatively to space the interval between consuming such foods and drug intake. The list also serves to dispel some myths about the mineral content of some foods, for example spinach, does not rank among the ten foods with highest Fe content, and liquid cow's milk is not among the ten foods with the highest Ca content.

**Table 6.** MINERAL CONTENT OF COMMON FOODS. THE TOP TEN FOODS WITH THE HIGHEST MINERAL CONTENT IN EACH CLASS ARE LISTED. ALUMINUM IS NOT INCLUDED SINCE THE FOOD CONTENT LARGELY DEPENDS ON PACKAGING OR COOKING UTENSILS\*

Foods high in mineral content (mg/100 g)

**Copper**

- goose liver (4.9)
- cal liver (4.4)
- cocoa, dried powder (3.9)
- oysters (3.7)
- mussels (3.2)
- lobster (2.2)
- beef liver (2.1)
- molasses (1.9)
- mushrooms (1.8)
- cheese (Edam) (1.7)

**Calcium**

- buttermilk, dried, non-fat (1300)
- cheese (Emmental) (1180)
- cheese (Parmesan) (1140)
- cheese (Edam) (765)
- cheese (Cheddar) (750)
- cheese (Roquefort) (700)
- scones (620)
- cheese (processed) (547)
- sardines, drained, solids (437)
- Ovaltine, dried powder (360)

**Iron**

- Ovaltine, dried powder (23)
- pork liver (19)
- cocoa, dried powder (12.5)
- caviar (11.8)
- lamb's liver (10.9)
- wheat germ (9.4)
- soybean flour, medium fat (9.1)
- egg yolk, whole dried (8.7)
- lentils (8.6)
- chicken liver (7.9)

**Zinc**

- oysters (6–100)
- oatflakes (14)
- pine nuts (14)
- wheat germ (13)
- beef liver (7.8)
- corn flakes (7.7)
- beef, canned, corned (5.6)
- wheat flour, whole (5.5)
- egg, whole, dried (5.0)
- cheese (Emmental) (4.6)

**Magnesium**

- cocoa, dried powder (420)
- wheat germ (336)
- soybean flour (medium fat) (290)
- almonds (dried) (270)
- pine nuts (268)
- cashew nuts (267)
- Brazil nuts (225)
- chick peas (160)
- broad beans (159)
- pistachio nuts (158)

**Sodium**

- beef, dried, salted (4300)
- ham, smoked, raw (2530)
- olives, green in brine (2400)
- caviar (2200)
- salmon, smoked (1880)
- salami sausage (1850)
- bacon (1770)
- pretzels (1680)
- cheese (Roquefort) (1420)
- Bologna sausage (1300)

**Potassium**

- cocoa, dried powder (900–3200)
- soybean, flour full-fat (2030)
- buttermilk, dried, non-fat (1745)
- molasses (1500)
- onions, dried (1380)
- kidney beans (1310)
- broad beans (1210)
- Ovaltine, dried powder (1200)
- potato chips (1190)
- peaches, dried (1100)

\*Source: Geigy Scientific Tables (164) from which more detailed information is available.

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# CHAPTER 16

## Recent and Unconfirmed Drug Interactions

These interactions were published in the medical or pharmaceutical literature whilst the bulk of this book was being printed and assembled. A note for guidance on the investigation of drug interactions was published by The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP) in March 1997, and permission has kindly been given by Mr Fernand Sauer, Director European Medicines Evaluation Agency (EMEA) for this text to be reprinted in this volume as Annex 1.

<i>Combination</i>	<i>Interaction</i>
<b>Aspirin/<i>Ginkgo biloba</i></b> (1)	The dietary supplement <i>Ginkgo biloba</i> may interact with aspirin causing bleeding problems. Bleeding from the iris into the anterior chamber of the eye (hyphema) has been reported in a 70-year-old patient. The patient reported recurring, 15 min episodes of blurred vision involving red discolouration. One week earlier he had started taking a supplement containing 40 mg concentrated extract of <i>Ginkgo biloba</i> twice daily. His only other medicine was aspirin 325 mg daily which had been taken for 3 years following cardiac bypass surgery. The patient stopped the supplement and no further problems occurred over a 3 month follow-up. One of the components of <i>Ginkgo biloba</i> extract is ginkgolide B, a powerful inhibitor of platelet activating factor. There are previous reports of subdural haematoma and increased bleeding time with

*Combination**Interaction*

**Aspirin/*Ginkgo biloba* cont.**

long-term use of the extract (2, 3), which is marketed as a supplement to improve mental alertness and to treat peripheral vascular disease. This report suggests that there may also be short-term effects.

**Bromfenac/phenytoin (4)**

An open-label, non-randomized, multiple-dose, inpatient study was conducted in 12 healthy male volunteers to compare the pharmacokinetics of the non-narcotic analgesic bromfenac and the anticonvulsant phenytoin when the drugs were given individually and concomitantly. Volunteers received multiple oral doses of bromfenac for 4 days and then oral phenytoin for up to 14 days, followed by concomitant administration of the two drugs for 8 days. Concomitant administration of the two drugs caused an approximate 40% decrease in the mean peak plasma concentration ( $C_{max}$ ) and the interdose area under the concentration-time curve (AUC) of bromfenac. The oral clearance ( $Cl_{po}$ ) of bromfenac doubled and the volume of distribution increased by 77%. For phenytoin, the mean peak serum concentration and the AUC increased by 9 and 11%, respectively, in the presence of bromfenac. The only change in unbound phenytoin was a 16% increase in the AUC. Although statistically significant, the changes in the pharmacokinetic parameters of phenytoin and unbound phenytoin were small. Adjustments in the dose of phenytoin were thought not to be required during concomitant administration of bromfenac, although each patient's clinical status should be evaluated individually.

**Cyclosporin/fluconazole  
griseofulvin  
ketoconazole  
terbinafine**

Cyclosporin is metabolized in the liver by the microsomal cytochrome P450IIIA subfamily (5). Coadministration of drugs that interact with this enzyme system may either induce or inhibit the metabolism of cyclosporin thus causing subtherapeutic or toxic cyclosporin levels. Fungal infection of the skin is very common in transplant patients, but the existing antifungal drugs (fluconazole griseofulvin, ketoconazole) are all reported to affect cyclosporin metabolism in transplant patients (6–8). Terbinafine, a

*Combination**Interaction*

new synthetic fungicidal agent, is effective in treating fungal infections of the skin and nails (9). It does not inhibit the cytochrome P450 system *in vitro* (10) and the interaction with cyclosporin was minimal in normal volunteers (11). Terbinafine (250 mg/day) was administered to four renal transplant patients receiving cyclosporin; trough cyclosporin levels were lowered. In three patients this drop was small and no change was required in the cyclosporin dosage level. In the fourth case, cyclosporin dosage was increased (stepwise from 3.6 to 6.5 mg/kg/day) in view of subtherapeutic levels of cyclosporin. Nevertheless, the overall magnitude of the change in cyclosporin level was less than that reported for the interaction between cyclosporin, griseofulvin, ketoconazole or fluconazole (7-9). Terbinafine given for 4 to 24 weeks was effective in clearing up the dermatophyte infection in all four cases and renal function remained stable during this therapy. It was emphasized that it was still necessary to monitor the cyclosporin level in patients whose drug levels were at the lower end of the therapeutic target.

**Cyclosporin/  
H<sub>2</sub>-antagonist  
cimetidine, ranitidine**

The literature does not support a pharmacodynamic interaction between H<sub>2</sub>-antagonists and cyclosporin that would result in potentiation of cyclosporin's nephrotoxicity. The increase in serum creatinine associated with cimetidine, in the majority of cases, is due to competition with creatinine for tubular secretion. Both cimetidine and creatinine are organic bases secreted in the proximal tubule. Ranitidine is unlikely to produce a change in serum creatinine. Additionally, there is no support for a pharmacokinetic interaction. However, cimetidine may influence peak concentrations of cyclosporin. Apart from the clinical evidence cited in this review article (12) two abstracts concur with these findings (13, 14). There is no information from the literature or from the manufacturers regarding interactions between cyclosporin and either famotidine or nizatidine that potentiate nephrotoxicity in transplant patients. Thus, interpretation of renal function may be confusing with concomitant administration of cimetidine and

<i>Combination</i>	<i>Interaction</i>
<b>Cyclosporin/ H<sub>2</sub>-antagonist</b> cont.	cyclosporin unless the glomerular filtration rate is accurately monitored. On the basis of the information currently available, ranitidine may be considered the H <sub>2</sub> -antagonist of choice in a patient treated with cyclosporin.
<b>Erythromycin or dirithromycin/cyclosporin, terfenadine theophylline warfarin (see review 15)</b>	Erythromycin, is metabolized by the cytochrome P450 enzyme system. By decreasing their metabolism, erythromycin can interact with other drugs metabolized by the same enzyme system. Since the lack of such interactions would be a desirable feature in a newer macrolide, studies were performed to detect any interaction of dirithromycin with a range of drugs. Dirithromycin, a new macrolide, did not inhibit the cytochrome P450 enzyme system. It contrast to erythromycin or clarithromycin, dirithromycin did not cause any significant changes in the pharmacokinetics of cyclosporin, theophylline, terfenadine or warfarin. However, in patient taking low-dose ethinyl oestradiol, the administration of dirithromycin caused a significant increase (9.9%) in the clearance of the oestradiol. Women with low ethinyl oestradiol bioavailability and increased gastrointestinal transit time may be at risk of contraceptive failure with this interaction.
<b>Ethinyl oestradiol</b>	
<b>Glibenclamide/rifampicin (16)</b>	Twenty-nine well controlled diabetic patients on a combination therapy of diet and glibenclamide, and willing to participate in the trial, received a daily dose of 450 mg (body weight <50 kg) or 600 mg (body weight >50 kg) of rifampicin for 10 days. There was a significant worsening of fasting and post-prandial blood sugar after administration of rifampicin. Dose modification of glibenclamide was required in 15 of the 17 patients in whom diabetes became uncontrolled. Blood sugar normalized by day 6 after stopping rifampicin in all patients. The mechanism of this interaction is induction of hepatic microsomal enzymes by rifampicin causing enhanced metabolism of glibenclamide. It was concluded that necessary dose modifications should be made to achieve euglycaemia if these two drugs are given together.

<i>Combination</i>	<i>Interaction</i>
<b>Glyburide/eprosartan (17)</b>	<p>The potential for eprosartan, a non-biphenyl tetrazole angiotensin II receptor antagonist, to affect the 24-hour plasma glucose profiles in type II diabetics treated with glyburide was investigated in a randomized, placebo-controlled, double-blind (eprosartan-placebo phase only), two-period, period-balanced, crossover study. All patients received a stable oral dose (3.75–10 mg/day) of glyburide for at least 30 days before the first dose of double-blind medication was administered. Patients were randomized to receive either 200 mg oral doses of eprosartan twice daily or matching oral placebo doses concomitantly with glyburide for 7 days during each treatment period. After a minimum washout period of 14 days, patients were changed over to the alternate treatment. Serial samples to measure plasma glucose concentrations were collected over a 24-hour period on the day before administration of eprosartan or placebo and again on day 7. Mean glucose concentrations were comparable between treatment groups before administration of eprosartan or placebo. The point estimate (90% confidence interval) for the ratio of the average mean 24-hour plasma glucose concentrations of eprosartan + glyburide to placebo + glyburide after 7 days of administration was 0.96 (0.90–1.01). Thus, it was concluded that eprosartan did not significantly alter the 24-hour plasma glucose profile in type II diabetic patients who had been previously stabilized on glyburide.</p>
<b>Imipramine and desipramine/ketoconazole</b>	<p>The effect of oral ketoconazole (200 mg/day for 14 days) on the kinetics of a single oral dose of imipramine (100 mg) and desipramine (100 mg) was evaluated in two groups of six healthy male subjects (18). This coadministration was associated with a decrease in imipramine apparent oral clearance from 1.16 to 0.96 h/kg (<math>P &lt; 0.02</math>), a prolongation in imipramine half-life from 16.7 to 19.2 h (<math>P &lt; 0.05</math>) and a decrease in AUC of metabolically derived desipramine from 3,507 to 3,180 nmol/l/h (<math>P &lt; 0.05</math>), whereas concentrations of 2-hydroxy-imipramine were unaffected. In the subjects given desipramine, no</p>

<i>Combination</i>	<i>Interaction</i>
<b>Imipramine and desipramine/ketoconazole cont.</b>	significant changes in desipramine and 2-hydroxy-desipramine kinetics were observed during ketoconazole treatment. These findings indicate that ketoconazole, a relative specific inhibitor of CYP3A4, inhibits the N-demethylation of imipramine without affecting the 2-hydroxylation of imipramine and desipramine. This interaction confirms that CYP3A4 plays a role in the demethylation of tricyclic antidepressants. The authors of this report believe that this interaction is unlikely to have clinical significance due to the relatively wide therapeutic range of imipramines steady-state plasma concentrations (150–250 µg/l) (19) and to the limited degree of inhibition of imipramines metabolism (about 20%).
<b>Lamotrigine/valproate (20)</b>	The manufacturers have alerted health professionals to new data indicating a severe skin reaction in children receiving its anti-epileptic drug lamotrigine. The risk of severe, potentially life-threatening reactions, including the Stevens–Johnson syndrome and toxic epidermal necrolysis, may be very much higher in children aged 12 years or under than in adults. The estimated incidence of reactions in children requiring hospital admission is between 1 in 300 and 1 in 100 patients. In adults the risk is around 1 in 1,000. The majority of skin reactions occur at the start of treatment (within 2 to 8 weeks) but some cases have been reported after prolonged treatment. The majority of patients recover after drug withdrawal, but some cases have experienced irreversible scarring and there have been rare cases of associated death. In addition to age, apparent risk factors associated with skin reactions include concomitant use of valproate (which increases the mean half-life of lamotrigine) and high initial doses of lamotrigine and exceeding the recommended dosage.
<b>Midazolam/fluconazole (21)</b>	Midazolam, a widely used short-acting hypnotic, is extensively metabolized by intestinal and hepatic CYP3A4 enzyme. Orally ingested imidazole antimycotics, including fluconazole, interfere with the metabolism of oral midazolam during its absorption and elimination

*Combination**Interaction*

phases. A study has compared the effect of oral and intravenous fluconazole on the pharmacokinetics and pharmacodynamics of oral midazolam in healthy volunteers. Results showed that both oral and intravenous fluconazole significantly increased the  $C_{max}$ , the  $t_{1/2}$ , and the AUC values of midazolam as well as its pharmacodynamic effects. The metabolism of midazolam was more strongly inhibited by oral than intravenous dosage of fluconazole, thus suggesting the role of intestinal drug metabolism in the interaction.

**Persona contraceptive system/tetracycline (22)**

The manufacturer of Persona contraceptive system (Unipath) has warned women that it should not be used if they are taking tetracycline since it may affect the accuracy of the test. Persona detects a woman's fertile period by measuring levels of luteinizing hormone and oestrone-3-glucuronide (an oestradiol metabolite) in urine. Tests have shown that, in some women, tetracycline can increase the level of luteinizing hormone. Women using Persona should use a barrier contraceptive if they are prescribed a short course of tetracycline. If they are taking tetracycline for more than a month, Persona should not be used. The problem is only with tetracycline, related antibiotics, including oxytetracycline, do not affect the test.

**Terfenadine/imidazole antifungals, macrolide antibiotics, grapefruit juice**

Terfenadine, until recently an OTC Pharmacy medicine, is a non-sedating antihistamine which is widely used without adverse effects. It is a pro-drug which is converted to fexofenadine as it passes through the liver after absorption from the gut. Generally, it is fully metabolized on its first pass and is not present in the systemic circulation. However, if metabolism is inhibited or overloaded, the parent drug reaches the circulation and prolongs the electrocardiograph QT interval. This predisposes to ventricular arrhythmias, particularly *torsade de points*, which may progress to ventricular fibrillation and death. Terfenadine should not be taken by patients with cardiac or hepatic disease and it should not be taken at the same time as a number of other drugs (e.g. ketoconazole,

*Combination***Terfenadine/imidazole antifungals, macrolide antibiotics, grapefruit juice cont.***Interaction*

itraconazole and related imidazole antifungals, erythromycin, clarithromycin and related macrolide antibiotics) or with grapefruit juice. In letters posted to doctors and pharmacists on 23 April 1997, the Chairman of the Committee on Safety of Medicine (Professor M. Rawlins) said that the CSM had recently reviewed the safety of terfenadine in relation to cardiac arrhythmias and was concerned that serious adverse reactions to terfenadine continued to be reported. The UK Medicines Control Agency has therefore announced that it is taking steps to make terfenadine a prescription only medicine (POM) (23). The FDA in the United States has announced its intention to remove products containing terfenadine from the US market following the successful introduction in the US of fexofenadine, a metabolite of terfenadine, which is claimed to provide the beneficial effects of terfenadine without the cardiotoxic risk (24). The French Health Authority has suspended marketing of terfenadine for 1 year (25).

**Warfarin/miconazole gel (26)**

The use of miconazole gel in a 73-year-old man resulted in loss of anticoagulant control. He had been given (26) warfarin 2 years previously after coronary bypass surgery and his condition was well controlled with 1–3 mg daily. He was prescribed miconazole oral gel 125 mg (5 ml) four times daily for oral candidiasis. Before this his international normalized ratio was 1.5. When repeated 2 weeks later, while using the oral gel, it was over 10. The miconazole gel and warfarin were immediately withdrawn and 2 weeks later the INR had reduced to 3. Warfarin was reintroduced at 2 mg daily and the ratio remained well controlled in the range 2–3. Two previous cases of this interaction have been reported (27, 28).

**Nicoumalone phenindione**

Potentiation has also occurred with the oral anticoagulants nicoumalone (29, 30) and phenindione (31). Together they indicate that the oral gel may be sufficiently absorbed to interact with other drugs. The BNF now contains such an appendix warning.

**Meloxicam/diuretics, and other agents (32)**

This NSAID should be used with caution in those patients taking diuretics, or who have recently undergone major surgery leading to hypervolaemia; monitor urine output and renal function in such patients. Use with caution in concomitant administration with other NSAIDs, anticoagulants, ticlopidine, lithium, methotrexate, IUDs, cyclosporin, antihypertensives, thrombolytics, and oral antidiabetics.

**Risperidone/levodopa and other dopamine agonists (33)**

Caution should be exercised when treating patients with Parkinson's disease or epilepsy. The antipsychotic, risperidone (Risperdal), may antagonize the effect of levodopa and other dopamine agonists. Drugs with dopamine antagonistic properties have been associated with tardive dyskinesia. If signs or symptoms of this appear then consider discontinuation of all antipsychotic agents.

**Carbamazepine (33)**

On initiation of carbamazepine or other hepatic-enzyme inducing drugs, the dosage of risperidone should be re-evaluated and increased if necessary; on discontinuation of such drugs, the dosage of risperidone should be re-evaluated and decreased if necessary.

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# **ANNEX 1**

The European Agency for the Evaluation of Medicinal Products  
*Human Medicines Evaluation Unit*

London, 17 March 1997  
CPMP/EWP/560/95

## **COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)**

### **NOTE FOR GUIDANCE ON THE INVESTIGATION OF DRUG INTERACTIONS**

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	June/October 1996 February 1997
TRANSMISSION TO THE CPMP	March 1997
TRANSMISSION TO INTERESTED PARTIES	March 1997
DEADLINE FOR COMMENTS	September 1997

## **THE INVESTIGATION OF DRUG INTERACTIONS (CPMP/EWP/560/95)**

This Note for Guidance should be read in Conjunction with the following:

- The CPMP guideline for Good Clinical Practice
- The CPMP guideline on Investigation of Bioavailability and Bioequivalence
- The CPMP guideline on Pharmacokinetic Studies in Man
- The CPMP guideline on Analytical Validation
- The CPMP guideline on Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products
- The CPMP guideline on Investigation of chiral active substances
- The CPMP safety guideline on Pharmacokinetics and Metabolic Studies in the Safety Evaluation of New Drugs in Animals
- The CPMP safety guideline on Repeated Dose Toxicity
- The CPMP safety guideline on Single Dose Toxicity
- The CPMP guideline on clinical investigation of medicinal products in children
- The CPMP guideline on fixed combination products.

### **1. INTRODUCTION**

As a consequence of the scientific development within the areas of pharmacokinetics (particularly drug metabolism) and pharmacodynamics, the focus of interaction studies has changed from ad hoc observational studies to rationally designed studies. Depending on the chemical characteristics and in vitro data, selective in vivo studies are performed. Based on results from such studies, the risk of clinically relevant interactions may be predicted. As a consequence, the information provided to the prescriber has also become more detailed and scientific.

The objectives of this Note for Guidance is to:

- outline requirements for interaction studies on new chemical entities on the basis of their physico-chemical properties, pharmacokinetics and pharmacodynamics.
- propose a structure for the presentation in the SPC of the information obtained.

In addition, the guideline is aimed at defining the in vivo studies needed and thereby reduce the number of preclinical and clinical studies.

In this document, an 'interaction' is defined as an alteration either in the pharmacodynamics and/or the pharmacokinetics of a drug, caused by concomitant drug treatment, dietary factors or social habits such as tobacco or alcohol. Other factors that may interact to alter drug disposition such as age, gender, activity, and time of administration will not be discussed in this guideline.

## 2. CLINICALLY RELEVANT INTERACTIONS

It is important in the drug development phase to differentiate between potential interactions and clinically relevant interactions.

An interaction is 'clinically relevant':

- when the therapeutic activity and/or toxicity of a drug is changed and
- when concomitant use of the two interacting drugs is likely to occur when used as therapeutically recommended.

To appreciate fully the potential of a new drug for clinically relevant interactions, the following aspects should be taken into account during the drug development program:

- Extensive characterisation of the physico-chemical properties of the drug.
- Early characterisation of the full pharmacodynamic profile and pharmacokinetic properties of the drug and the factors that may alter these.
- In vitro data should mainly be used qualitatively due to the uncertainty regarding in vitro/in vivo correlation. Thus, based on in vitro data, applicants should design and perform relevant in vivo studies.
- Preferably, both pharmacokinetic and when relevant pharmacodynamic variables should be studied in the in vivo interaction studies. The clinical relevance of the results for the in vivo studies should be discussed in light of the dose-concentration-effect (therapeutic as well as toxic) relationships for the drug.
- The studies should focus both on effects of other drugs on the drug under investigation and vice versa.
- Generally, in vivo studies will be required to support a claim of "No clinically relevant interactions" in the SPC.

## 3. PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic actions may include both therapeutic and adverse effects of drugs. Extensive pharmacological and toxicological knowledge about the drug is crucial for the performance of a meaningful pharmacodynamic interaction study.

Pharmacodynamic interactions may be caused by a large variety of mechanisms. It is therefore impossible to give detailed guidance for pharmacodynamic studies, where the design must be determined on a case-by-case basis. When similar, mechanisms and/or effects are found in animals and in humans, animal studies can be used to characterise a potential interaction. In general, animal, in vitro and clinical studies together will better describe the pharmacodynamic interaction profile of a drug.

Pharmacodynamic interactions studies should be performed:

- when drugs likely to be coadministered have similar or opposing pharmacodynamic effects.

- when drugs likely to be coadministered have potentially similar interacting mechanisms.
- when structurally similar compounds are known to interact with certain other compounds
- In addition, such studies might be warranted for any compound which is to be commonly used together with the compound under investigation due to standard therapeutic recommendations.

When designing pharmacodynamic studies, it must be remembered that:

- An interaction may be due to direct competition at a particular site of action or could be indirect involving altered physiological mechanisms or sensitivity of the systems affected.
- Both the therapeutic and the toxic effects can be altered by pharmacodynamic interactions.
- Pharmacodynamic interactions may involve interaction between therapeutic activity of one compound with toxic effect of another compound.
- Therapeutic activity and toxic effect might be affected in different directions resulting in a modified balance between positive and negative properties,

## 4. PHARMACOKINETIC INTERACTIONS

### 4.1. Absorption

This guideline focuses on absorption interactions in the gastro-intestinal tract. Absorption interactions may, of course, occur at absorption sites e.g. following dermal or nasal administration. It should be noted that a drug given by another route of administration, e.g. the intravenous route could have an impact on the gastro-intestinal absorption, by its pharmacodynamic effect on, e.g. gastro-intestinal secretion or motility.

In the case of an interaction, rate of absorption, fraction absorbed and first-pass metabolism may be influenced. Normally, a change in the bioavailability is of particular clinical importance.

In vitro studies may be helpful in investigating transport mechanisms or the potential of a drug for complex binding/chelation. However, potential interactions should be studied *in vivo* in humans since in vitro absorption studies have been shown to be of limited value.

When deciding on absorption studies needed, the following should be considered:

- Effect of food and antacids should always be studied with new drugs intended for oral administration or with new modified release dosage forms.
- Other absorption interaction studies should be performed if:
  - the dissolution of the drug in question is pH-sensitive
  - one of the drugs is known to alter gastric pH
  - there is high prevalence of gastrointestinal mucosal disease in the target population.

When designing absorption interaction studies, it must be remembered that:

- Food-related interactions should preferably be investigated early in drug development process so that the information obtained may be considered in the design of the Phase II and III studies.
- Food or other drugs may influence drug absorption for several hours. If a significant interaction is demonstrated, the dosage recommendations (i.e. timing of dose in relation to the interacting agent) should be adequately validated in the clinical situation.
- Dosage forms sensitive to food effects should be avoided if possible. It is therefore important to determine if the food/drug is influencing the drug substance and/or the dosage form.
- Factors/mechanisms causing the interaction should be identified wherever possible.

#### **4.2. Distribution**

Displacement of drug from plasma proteins is the most common explanation for altered distribution in drug interactions. However, few displacement interactions result in clinically relevant changes.

Displacement interaction studies should be performed when the investigated drug:

- has a narrow therapeutic index and
- is highly bound (>90%) to proteins in human plasma at therapeutic concentrations and
- is highly protein bound (>95%), and occupies most of the binding sites (e.g. plasma therapeutic concentrations at the highest recommended dose exceed the plasma binding capacity).
- at single dose or initiation of therapy (starting or loading dose) when the volume of distribution of the investigated drug is small (<10L/70 kg).
- when the investigated drug is administered intravenously and possesses a high metabolic extraction ratio.

When designing displacement interaction studies, it must be remembered that:

- Displacement studies should be performed in vivo, since the metabolites of the drug may also be involved in such interactions.
- Unbound peak plasma concentration should be determined by estimation of the unbound fraction at at least three time points.
- Changes in unbound plasma concentration may not occur in parallel with the total plasma concentration.
- The methods used must be well documented and validated.

### 4.3. Elimination

The majority of known clinically relevant interactions is due to changes in the elimination of drugs. Therefore, information of immediate interest early in the development of a new drug is the relative clearance by metabolic and non-metabolic routes.

#### 4.3.1. Metabolism

The primary metabolic pathway(s) for the drug, and the proportion of the total clearance, that each primary metabolic pathway constitutes should be determined at an early stage. Furthermore, the enzyme(s) responsible for the metabolism, possible polymorphism in the metabolism, inhibiting and inducing potential for the drug should be investigated. In Table 1 major drug metabolising CYP450 enzymes are listed (appended).

Depending on the properties of the drug, and the route of administration, different effects on the unbound plasma concentration could be expected when the intrinsic clearance or the liver blood flow are changed. Furthermore, it has to be taken into account that the outcome of metabolic drug interactions could be more serious in cases of steep concentration-response curves.

##### 4.3.1.1. Change of intrinsic clearance

An inhibition or induction of the metabolism resulting in a change of the intrinsic clearance cause a change of the unbound plasma concentration at steady state for “low extraction drugs” administered orally or i.v., and for “high extraction drugs” administered orally. On the other hand, there is no change of the unbound plasma concentration at steady state for “high extraction drugs” administered i.v.

###### 4.3.1.1.1. Metabolic induction

Clinically relevant induction occurs during chronic exposure to the inducing drug and is a dose and time dependent phenomenon.

Points to consider regarding metabolic induction:

- Decide if the defined enzyme(s), is (are) inducible or not.
- Some time is required for the onset and offset of induction.
- When metabolites are pharmacologically active, it should be remembered that the introduction of an inducer leads to decrease in the pharmacological activity(ies) of the parent drug, but an increase in that of the metabolites.
- The clinical effects of induction might be more serious when the inducer is abruptly withdrawn.
- Many dietary and social habits e.g. smoking or charcoaled meat may induce drug metabolism.

#### 4.3.1.1.2. Metabolic inhibition

Inhibition is also a dose dependent phenomenon but in contrast to induction, clinically relevant inhibition occurs readily. In inhibition processes, both the oxidative system, the hydrolyses and the conjugation system may be involved.

Points to consider regarding metabolic inhibition:

- Most inhibition is competitive and disappears rather rapidly as soon as the inhibitor is eliminated or decreases after the dose is reduced.
- Opposite to induction, inhibition is often enzyme specific.
- When metabolites are pharmacologically active, it should be remembered that the introduction of an inhibitor leads to an increase in the pharmacological activity(ies) of the parent drug but a decrease in that of the metabolites.
- Some dietary constituents are known inhibitors of drug metabolism e.g. grape fruit juice.

#### 4.3.1.1.2. Change or blood flow

In general, a change of the blood flow through the liver causes no change of the unbound plasma concentration at steady state for “low extraction drugs” administered orally or i.v., and for “high extraction drugs” administered orally. On the other hand, a change of the unbound plasma concentration at steady state for “high extraction drugs” can be expected ‘if administered i.v.’

#### 4.3.1.1.3. Metabolic interaction studies

Metabolic interaction studies should be performed:

- for drugs where metabolism is the prominent route of elimination
- for orally administered drugs with low bioavailability due to extensive first pass metabolism.
- when a specific enzyme is responsible for more than 30% of the total clearance of a drug.

When designing metabolic interaction studies, it must be remembered that:

- The enzyme kinetic parameters ( $K_i$ ,  $K_m$  and  $V_{max}$ ) should be determined preferably by kinetic modelling.  $K_m$  allows prediction of the potential of the drug as a competitive inhibitor of the metabolism of other drugs by a particular enzyme, and is also used to define the potential of other drugs to inhibit the metabolism of the new drug. The likelihood for a potential in vivo interaction depends on the relative  $K_i$  and  $K_m$  of the two drugs involved, and their relative in vivo concentrations.
- Define the potential of the new drug to inhibit drug metabolising enzymes including important enzymes for which the drug is not a substrate. The  $K_i$  for potent interactions should be determined to allow in vivo predictions.
- The interactions predicted from in vitro data should be confirmed in vivo.

These in vivo studies should consider the therapeutic index of drugs likely to be coadministered.

- at least one of the potent inhibitors of the specific enzyme should be studied.
- If the drug is extensively metabolised, but specific enzymes are unknown, possible interactions should be studied with generally known “probe” inhibitors/inducers.

#### **4.3.2. Renal excretion**

Interactions at the level of renal excretion have been reported for many drugs where renal excretion is the dominant route of elimination. The role of renal elimination in the excretion of active metabolites is just as important in the context of such interactions.

For drugs where the renal route is an important route of elimination, interactions could occur via changes in urinary pH and/or urinary flow rate, resulting in changes in the passive reabsorption, and by competition of active secretion in the renal tubule.

Renal excretion interaction studies should be performed:

- when the renal elimination is the prominent route of elimination of either parent and/or pharmacologically active or toxic metabolites and
- when the drug/active or toxic metabolite is excreted by active secretion or there is an indication of significant reabsorption.

When designing renal excretion interaction studies, it must be remembered that:

- The alteration of pH is only clinically significant if the  $pK_a$  value of the drug is in the range of about 7.5–10.5 for bases, and 3.0–7.5 for acids.
- Of the two secretion pathways, the one for acids appears clinically to be the more important pathway for interactions.
- The potential for interactions involving active renal secretion could be studied using in vitro methods.

Examples of drugs actively secreted into the renal tubule is given in Table 2.

#### **4.3.3. Hepatic/biliary excretion**

For drugs where the biliary route is an important route of elimination, and for which a saturation of the excretory capacity of the liver is possible, interactions caused by competition for hepatic excretion should be considered. Interactions at the level of hepatic excretion have been reported for a few drugs (e.g. rifampicin).

## **5. POINTS TO CONSIDER WHEN DESIGNING AND ASSESSING INTERACTION STUDIES**

One advantage of performing drug interaction studies early in the drug development process is that knowledge of causes for variability, such as food interactions, could be considered in the design of Phase II and Phase III studies. Thus, extensive investigation of potential interactions at an early stage of drug development is encouraged.

### **5.1. Mechanism based in vivo studies**

When studying the effects of inhibition or induction on the pharmacokinetics or pharmacodynamics of a new drug, the following should be considered:

- in vivo pharmacokinetic interaction studies could most of the time be performed in healthy volunteers, while in vivo pharmacodynamic interaction studies would preferably be performed in patients. Disease-related interactions should always be considered.
- Subjects participating in metabolic in vivo interaction studies should be appropriately phenotyped if any of the active enzymes mediating the metabolism are polymorphically distributed in the population. In some cases, clinically relevant interactions may only occur in a subset of the total population, e.g. for slow-metabolisers when an alternate route of metabolism is inhibited.

#### **5.1.1. Experimental design**

When designing interaction studies it must be remembered that:

- the pharmacokinetic parameters of the inducer or the inhibitor should be carefully considered and steady state conditions be achieved whenever possible. Approved therapeutic dose regimen for the selected inhibitor or inducer may not be optimal enough to obtain a full inhibitory or inducing effect. The number of daily doses may have to be increased to ensure inhibition/induction during 24 hours. Similarly, the duration of pre-treatment with an inducer should be sufficient to maximise the influence on the metabolic system.
- sufficient time must be allowed to reach a pharmacokinetic steady-state.
- the properties of the drugs should be considered in the choice of study design.
- In order to reduce variability, a cross-over design is usually the first choice. Other designs may be chosen in specific situations, but should be justified in the study protocol. The design of the studies should include randomisation, and whenever possible double-blind.
- In studies involving simple induction or inhibition, it may be adequate to investigate the effect of one drug on the pharmacokinetics of the drug in question. However, when the two drugs are substrates of the same enzyme, it is important to investigate the pharmacokinetics of both the drugs adminis-

tered singly and in combination to the same cohort in order to evaluate the effect of each drug on the other.

- In most in vivo pharmacokinetic studies it seems reasonable to focus on the exposure of the drug, AUC and the two variables determining this, i.e. extent of absorption, F, and clearance (Cl). Other parameters may also be of interest such as  $C_{max}$  and  $t_{1/2}$ .
- The number of subjects should always be justified. Since the aim often is to demonstrate that there is no clinically relevant interaction, special attention should be paid to the risk for a Type II error, i.e. the risk for not detecting a relevant interaction.
- the precision of the estimate of the size of any potential interaction must be considered.

### **5.1.2. Statistical analysis**

In the statistical analysis it should be remembered that:

- The statistical analyses of the main treatment effects of interest should in general be carried out by means of analysis of variance and should include the calculation of confidence intervals for the estimates of the size of the effects.
- To demonstrate the lack of a relevant interaction, the currently accepted bioequivalence approach (i.e. the inclusion of the 90% confidence interval for the ratio/difference of the means within some prespecified equivalence range) may be appropriate.
- If this fails, the point estimate together with the confidence interval should form the basis for any potential recommendations of dose modifications.

These methods for comparison of means are appropriate in most situations. However, the consequence of an interaction might be increased variability and for drugs with a narrow therapeutic index designs and methods that focus on analysis of variability might be necessary. The statistical analysis of variability needs special attention.

### **5.1.3. Interpretation of mechanism based studies**

It seems reasonable that in vivo studies with inducers/inhibitors may be used to extrapolate to other inducers/inhibitors of the same enzyme. Similarly, effects of the new drug on substrates should be transferable to other substrates for the same enzyme.

## **5.2. Population pharmacokinetic studies**

It is often valuable to include a population approach in Phase II/III clinical trials to screen for pharmacokinetic drug interactions. Valuable additional information is then obtained from studies that are performed for other reasons. It is, however,

important to remember that in the context of the population approach, these studies are not randomised and may therefore be subject to the usual bias of observational studies. The outcome should mainly be used as hypothesis-generating and the best use of this approach can probably be made to highlight unsuspected interactions and possibly to confirm absence of suspected interactions. The successful use of such an approach is highly dependent upon the protocol inclusion criteria so that

- sufficient numbers of patients taking the potentially interacting drug exist (to avoid falsely not finding an interaction)
- information should be available as to when the interacting drug was taken, and should be within a reasonable time frame with respect to when the test drug was administered.

In order to avoid drawing incorrect conclusions, in particular false negative conclusions, certain aspects of analysis need special attention, because the statistical models and computational procedures used to analyse population pharmacokinetic studies can be particularly complex. It is important to ensure that the particular models chosen and procedures used are reliable, and are appropriate for the statistical distribution of the data. In addition, the influence of potential confounding factors, such as age, on the results and conclusions should be checked, bearing in mind the lack of randomisation and the possibility for bias.

A confidence interval associated with the estimate of the interaction should be presented. This is particularly important if no significant interaction is detected in order to permit an assessment of the degree of interaction potentially excluded.

## **6. INFORMATION IN THE SPC**

The information in the SPC should follow the general guideline outlined in the Notice to Applicants. However, the increased knowledge of factors influencing potential interactions and the possibility to study these factors in a selective mechanistic way also influences the way in which such information is provided to the prescriber. An information solely based on mechanisms is probably not sufficient and the information should be clarified with examples. Relevant information should be included under the headings as outlined below. As pointed out below, serious clinical interactions should also be described either under "4.3 Contraindications" or "4.4 Special warnings and precautions for use" in the SPC. It should also be noted that lack of knowledge regarding drug interactions is not only an issue for the SPC, but could for a given drug, influence the risk/benefit assessment in the final opinion.

### **6.1. Clinical particulars**

Examples of SPC-texts related to drug interactions are given below:

#### 4.3. Contraindications

*Drug X prolongs the QT interval and is contraindicated in patients treated with . . . . .*

#### 4.4. Special Warnings and Precautions for Use

*Drug X may prolong the QT interval and should be used with caution in patients concomitantly treated with . . . . .*

#### 4.5. Interactions

Results from performed in vivo studies in humans should be described under this heading together with potential interactions predicted from in vitro studies but not studied in vivo. It is important to clearly differentiate between effects of other drugs on the investigated drug, and effects of the new drug on other drugs. In vivo results showing lack of interaction could also be included when this information is valuable. The potential for renal interactions with other drugs has to be stated when the renal elimination is 50% of the total elimination.

The information could be worded as follows:

*Drug X is an inhibitor of CYP3A4 and has been shown to increase the levels of triazolam. Hence, caution is advised when X is given together with other substrates for CYP3A4 such as . . . . The pharmacokinetics of X were not influenced by the CYP3A4 inhibitor ketoconazole.*

*Drug X has been shown to induce serotonergic syndrome in combination with MAO-inhibitors. Treatment with Y should not begin until two weeks after the cessation of treatment with MAO-inhibitors.*

As mentioned above, the text should also discuss potential interactions which have not been addressed by the applicant. If relevant in vivo studies are not performed, the following text provides an example based on the results from performed in vitro studies:

*Although interaction studies have not been performed, due to the potential enzyme induction, drug X should not be combined with drugs which are metabolised by CYP1A2 and which exhibit a narrow therapeutic index, such as . . . .*

or

*Although interaction studies have not been performed, since this drug is metabolised by CYP3A4, it is expected that ketoconazole, itraconazole, grape fruit juice . . . . - inhibit the metabolism. On the other hand, inducers of this enzyme such as rifampicin, phenytoin . . . . may reduce the levels of the drug. Since the magnitude of an inducing or inhibiting effect is unknown, such drug combinations should be avoided.*

or

*The haemodynamic properties of digoxin, noradrenaline and adrenaline would be*

*expected to be potentiated in combination with drug Y. Hence, caution is advised if these drugs are given concomitantly.*

## **6.2. Pharmacology**

Relevant pharmacokinetic, metabolic and pharmacodynamic properties of the drug should be summarised under 5, e.g.

### **5.1. Pharmacodynamics**

*Drug X is an inhibitor of the reuptake of serotonin and noradrenaline.*

### **5.2. Pharmacokinetics**

*Drug X is mainly metabolised by CYP3A4 and has demonstrated a capacity to induce this enzyme and CYP1A2 in vitro.*

## 7. APPENDIX

**7.1. Table 1: The major drug metabolizing CYP450 enzymes, examples of substrates, inhibitors, inducers and markers.**

P450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS	MARKERS
CYP1A2	Acetaminophen Aromatic amines Caffeine Phenacetin Theophylline	Fluvoxamine Furafylline	Charcoal-broiled beef Cigarette smoke Cruciferous vegetables	Caffeine
CYP2C9	NSAID drugs Phenytoin Tolbutamide <i>S</i> -Warfarin	Sulfaphenazole Sulfinpyrazone	Rifampicin Barbiturates	<i>S</i> -Warfarin Tolbutamide
CYP2C19	Citalopram Diazepam Hexobarbital Imipramine Omeprazole Proguanil Propranolol	Tranylcypromine	Rifampicin Barbiturates	Mefenitoxin Omeprazole
CYP2D6	Several anti-depressants Neuroleptics Beta-blockers Antiarrhythmics Codeine Dextromethorphan Etylmorphine Nicotine	Ajmaline Chinidin Fluoxetine Paroxetine Quinidine Ritonavir	None known	Debrisoquine Dextromethorphan
CYP2E1	Acetaminophen Alcohols Caffeine Chlorozoxazone Dapsone Enflurane Theophylline	Diethylthiocarbamate Dimethyl sulfoxide Disulfiram	Ethanol Isoniazid	Caffeine Chlorozoxazone
CYP3A4	Acetaminophen Carbamazepine Cyclosporin Digitoxin Diazepam Erythromycin Felodipine Fluoxetine Nifedipine Quinidine Saquinavir Steroids (e.g. cortisol) Terfenadine Triazolam Verapamil Warfarin	Clotrimazole Ketoconazole Ritonavir Troleandomycin	Dexamethasone Phenytoin Rifampicin Troleandomycin	Dapsone Erythromycin Ketoconazole Lidocaine

**7.2. Table 2: Examples of drugs actively secreted into the renal tubule**

ORGANIC ACIDS	ORGANIC BASES
acetazolamide	amantadine
some cephalosporins	amiloride
chlorpropamide	cimetidine
hippuric acid	dopamine
indomethacin	ethambutol
loop diuretics	meperidine
methotrexate	metformin
oxyphenbutazone	N-methylnicotinamide
penicillins	morphine
phenylbutazone	procainamide
probencid	d-pseudo ephedrine
salicylic acid	quinacrine
sulphonamides	triamterene
sulphonic acids	
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# Index

This index is divided into two main parts. **Index A** deals with drugs and associated events. **Index B** contains a Table of Drug Incompatibilities (*in vitro*) and a Table of Drug Interactions (*in vivo*). In these tables individual pairs of interactants are listed in alphabetical order.

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