Royal Society of Medicine

President
The Rt Hon Lord Cohen of Birkenhead MD

Meeting April 9 1965

Symposium Number 7

Clinical Effects of Interaction Between Drugs

Section I

Chairman
The Rt Hon Lord Cohen of Birkenhead MD

Review of Points at which Drugs Can Interact

by Professor Alastair G Macgregor MD FRCP
(*Department of Materia Medica and Therapeutics, University of Aberdeen*)

Abstract
The prescribing of mixtures is unfortunately traditional and has a psychological appeal, which is being encouraged by many manufacturers. Doctors must have a sound working knowledge of the mode of action of modern drugs in order to use them effectively and safely, particularly when they are used together.

In this context 'drug' means any biologically active substance. Interaction between drugs can be inapparent (if equal and opposite), antagonistic or synergistic. This includes summation and potentiation.

Interaction between drugs can arise in a variety of ways: directly; in the intestine or other absorptive site; in transit; at the receptor or at another site in the same biological system; by accelerating or slowing drug metabolism; or by influencing excretion.

Most of these mechanisms are considered in detail in this Symposium. With greater understanding of underlying mechanisms many of the untoward interactions now being increasingly reported might be foreseen and avoided.

We are much concerned with drug interaction because doctors so often prescribe more than one drug at a time. This may not have mattered a hundred years ago when many of the agents were, pharmacologically, virtually inert. Nor perhaps was it of much consequence in 1785 when William Withering, in his clinical description of the advocated treatment for 'dropsy', suggested that this should include 'medicines of the de-obstruent, tonic, antispasmodic, diuretic and evacuate kinds'. Following his instructions involved the use of 'pills of Myrrh and white vitriol; and if costive, a pill with calomel and sloes'. It is quite obvious that then, and unfortunately now, as Jick & Chalmers (1964) have pointed out, there was a psychological appeal in prescribing 'not just one, but a combination of medically proven ingredients', and this appeal was, and still is, difficult to resist because of the inference that 'more' drugs are necessarily better than 'less' drugs; a conclusion which is very far from the truth. Jick and Chalmers (1964) reviewed issues of the *Journal of the American Medical Association* and showed that in 1950 there were, in two issues, 22 advertisements for orally administered drugs, of which only 2 had two or more ingredients. In two issues each in 1962 and 1964 there were 120 advertisements for oral medication, of which 52, nearly half, concerned combinations of two or more agents. Wilson (1962) showed that, of 169 new products introduced in Britain in 1961, a total of 113 (67%) were for products which were in effect combinations of drugs.

The tendency to prescribe several together of the many new potentially useful (but too often potentially harmful) remedies has encouraged the marketing of fixed ratio combinations. The major increases in new drugs have been in the fields of steroids, hypnotics, tranquillizers and analgesics, psychotropic drugs, hypotensives, diuretics and antibiotics; frequent indeed have been the temptations to prescribe drugs from these groups in combination. A recent study at Johns Hopkins Hospital showed that an average of 14 other drugs were prescribed, during their hospital stay, for patients who were given sodium methicillin, the range being 6–32 (Cluff 1964).

And thus have arisen our troubles. Many doctors, in this country and elsewhere, have simply not had the opportunity – or perhaps the desire – to inform themselves adequately about the pharmacological actions and hazards of many of the agents which they use. This they must do to be therapeutically efficient. Doctors have not been aware of the risks to which their patients were exposed with multiple drugs. Occasionally these risks are predictable, on the basis of known animal pharmacological observations, but too often they only become apparent after the exposure of many patients, often under inadequately controlled and observed conditions.

Before proceeding we must be clear what we mean by the term 'drug'. A widely acceptable definition is 'any biologically active substance', and this encompasses not only synthetic or naturally occurring chemical products but also hormones, neurohormones and substances administered for diagnostic as well as for therapeutic purposes.

Potential interaction between drugs may, of course, be of little significance or even quite inapparent, if the actions are opposite in nature and equal in strength. Some types of antagonism may be dangerous, or they may be merely inconvenient. On the other hand, synergistic actions of drugs may result from summated actions, which may be desirable if unwanted side-effects of each component can be 'filtered out'; or undesirable if unforeseen exaggeration of the desired effect occurs. Potentiated effects of drugs given in combination are not as frequently encountered as used to be believed. The term is used to describe actions which together are greater than the sum of the parts. Finally, the phrase 'drug interaction' can quite legitimately be applied to interaction between an administered drug, and a known or unknown component of a normal diet.

Strong (1962) showed that monoamine oxidase inhibitors could cause extraordinary side-effects in patients whose diet, or whose other treatment, contained catecholamines. Subsequently the demonstration by Blackwell (1963), and later by Professor Milne and his colleagues (Asatoor *et al.* 1963), that the combination of Brie cheese, containing tyramine, and tranylcypromine (Parnate) caused a hypertensive reaction was greeted with startled astonishment – and the withdrawal of tranylcypromine from the American, but not the British, market. This could have been predicted, and no harm done to patients, if some planned clinical pharmacological experiments had been conducted at an early stage. But this was not done, and the observations were made, in the end, by serendipity!

No longer is it possible for doctors to 'get by' with a modicum of knowledge about aspirin and atropine, digitalis and diuretics, hypnotics and hormones, penicillin and purgatives, for the hazards of drug therapy have increased with the increasing pharmacological activity of most modern therapeutic agents. This means that every doctor has to be knowledgeable before he uses drugs, and must continually educate and re-educate himself about the products that he uses. Sir John Gaddum and Sir George Pickering have been preaching for years that the treatment of every individual patient is a separate experiment, the results of which require objective analysis. This is particularly necessary on every occasion when two or more drugs are given together, and the observations made in man may well be of very much greater significance and importance than the previously recorded changes in animals.

How, briefly, can drug interaction occur? There can be a *direct* effect of one compound upon another, such as the intentional neutralization of heparin with protamine, or a chemical interaction of the nature of chelation such as is utilized in the management of lead poisoning. Alternatively, the *intestinal absorption* of drugs may be modified by procedures that alter the pH, or provide particular ions. The *transport* of a drug within the circulation may be affected by the concomitant administration of another drug that, perhaps, displaces it from a particular protein component. At the *receptor site* its action may be modified by physiological antagonists, such as the antagonistic effect of histamine and adrenaline, or by competition such as between adrenaline and phentolamine. The presence of one drug may accelerate or retard the *metabolism* of a second drug. Similarly, a second drug may affect the metabolism of a body cell or micro-organism in a certain way and perhaps block an alternative metabolic route already being used in the presence of the first drug. Lastly, the *excretion* of a drug may be accelerated or retarded by the administration of compounds that alter the urinary pH, or which, as probenicid retards penicillin excretion, have a direct effect upon the kidney.

Many of the reported interactions between drugs are due to drug metabolizing enzyme systems, particularly in the liver, being affected by previous administration of other drugs.

In animal species pretreatment with a drug may increase the activity of the enzyme system

responsible for metabolizing that drug, or drugs structurally related to it, but many examples exist where one drug inhibits the enzyme metabolic system responsible for disposing of another drug – thereby potentiating or prolonging the action of the other drug (La Roche & Brodie 1960). Pretreatment of rats with phenylbutazone (Butazolidin) will enhance the ability of the liver to metabolize phenylbutazone; or imipramine (Tofranil) pretreatment will enhance the ability of liver microsomes to metabolize imipramine. But the interest of such demonstrations lies in the extent of cross-stimulation or actual inhibition that may be determined. Pretreatment, for example, with nikethamide results in enhanced pentobarbitone (Nembutal) metabolizing activity in the liver (Brazda & Baucum 1961) and prior phenobarbitone administration augments zoxazolamine hydroxylase activity (Conney *et al.* 1961). It has been suggested that such augmenting actions are due to the stimulation of the synthesis of enzyme protein by polycyclic hydrocarbons and drugs, for several groups of workers have shown that this induction of increased microsomal enzyme activity is completely prevented by the amino acid antagonist, ethionine, which prevents the incorporation of methionine and glycine into liver protein.

Although this effect of drugs in accelerating or inhibiting the breakdown of another drug in rats need not necessarily apply in man, Dayton & Weiner (1961) have observed that prior barbiturate administration accelerates the breakdown of coumarin drugs in man, and many other examples come to mind. The importance of these remarks, however, lies in the realization that interspecies differences are huge, and the speed and pathway of metabolism of a drug in man may be very different from that which has been determined in many species of laboratory animal. For this reason Brodie (1962) has emphasized that if drugs appear to be potentially useful they must be studied in man at an early stage of their development. In saying this he implies that we should be in a position to make accurate measurements at an early stage but, as Modell has emphasized (1964):

'Trial in man is the only way of establishing drug interaction in man. If it is not performed in a regulated experiment, trials will be continuously performed in the clinical use of the new drug until all possibilities have been explored, and results collated. Commonly, the latter type of human experiment is carried out unwittingly by the physician on the unwitting patient, and, being unwitting, it is too often witless.'

I do not propose to discuss the extent to which factors such as age, or concurrent disease, may appear to promote drug interaction. Old people are particularly liable to get unfortunate interactions between digoxin and diuretics, which promote hypokalæmia, and the slower metabolism of digoxin in the elderly may result in marked potentiation of its action, with toxic effects, when even quite small doses are being given. Similarly concurrent liver or renal disease, limiting respectively the metabolism or excretion of a drug, may easily result in undesirable interactions.

Undoubtedly the most important fields where drug interaction may be of greatest inconvenience and danger are in the realms of psychopharmacology and cardiovascular pharmacology.

The monoamine oxidase inhibitors may perhaps have justified their introduction into the therapeutic armamentarium, but they are so frequently misused and abused that one wonders at times whether they really represent advance. Their interactions with narcotics and with sympathomimetic amines are numerous and frightening, and many of us believe that in most instances similar or better results can be obtained with imipramine or amitriptyline (Tryptizol) with less risk. The hypertensive crises that may be precipitated when amphetamine or related drugs are given, knowingly or unknowingly, at the same time, represent a real hazard, particularly when one appreciates that, according to the *Prescribers' Journal* (1965) there are available on the British market, on prescription, no less than 44 proprietary preparations containing amphetamine. Unfortunately many doctors do not appreciate that many of these preparations are dangerous to use with monoamine oxidase inhibitors, and, of course, with hypotensive drugs such as methyldopa (Aldomet) or guanethidine (Ismelin), whose effects may be antagonized.

Increasingly nowadays physicians are preoccupied with the manifestations of atherosclerosis and hypercholesterolæmia, and frequent may be the temptation to try to influence the natural history of the condition with clofibrate (Atromid S). Such patients, for one reason or another, may also require to have anticoagulants and here again one may find much lower doses tolerated in the patient receiving clofibrate.

I cannot catalogue all the ways in which the drugs we use may interact, but merely mention the more uncommon reactions of tolbutamide (Rastinon) and sulphonamides, of neomycin and tubocurarine. The dangers and risks to which the about-to-be anæsthetized patient is subject are manifold, if the anæsthetist is not fully informed

about previous use of steroids or stimulants, hypnotics or hypotensives.

I have already touched upon the possible effect of diet, in relation to cheese and monoamine oxidase inhibitors, and it may well be that some adverse effects of some of the drugs we use can be attributed to unknown components in the diet with which there is interaction, or perhaps they may, in some instances, be due to effects of deprivation of some dietary factor, which previously exerted a protective influence. West (1964) has recently shown that, when testing for the teratogenic activity of drugs in rats, the toxicity of aspirin was greatly increased in rats fed on a high carbohydrate, as against a high protein diet; furthermore, dietary magnesium deficiency produced a greatly increased fœtal mortality rate in the aspirin-treated animals, particularly those on the carbohydrate diet.

However, not all interactions are undesirable. They may be beneficial if the incidence of adverse reactions is appreciable with larger doses of the single drug. Or, again, an interaction may be the basis for the desired pharmacological activity, such as the enhanced oxidation of ethyl alcohol to acetaldehyde which occurs when alcohol is taken after disulfiram. The consequent discomfort and manifestations of toxicity are said to be helpful in the management of alcoholism.

Much research will continue to be conducted on the interactions in man of the drugs that we use, and no doubt, as in the past, we shall tell each other, with the wisdom given us by hindsight, that the reactions we discover could all have been predicted if we had adequately assimilated and collated and appreciated the mass of data already at our disposal. This may well be true, but the imperfections of our systems of research and communication of scientific information may well mean that we shall always depend on our retrospectroscopes to understand them.

REFERENCES

Asatoor A M, Levi A J & Milne M D (1963) *Lancet* **ii**, 733

Blackwell B (1963) *Lancet* **ii**, 414

Brazda F G & Baucum R W (1961) *J. Pharmacol. exp. Ther.* **132**, 295

Brodie B B (1962) *Clin. Pharmacol. Ther.* **3**, 374

Cluff L E (1964) *J. Amer. med. Ass.* **188**, 976

Conney A H, Michaelson I A & Burns J J (1961) *J. Pharmacol. exp. Ther.* **132**, 202

Dayton P G & Weiner M (1961) *Ann. N.Y. Acad. Sci.* **92**, 302

Jick H & Chalmers T C (1964) *Clin. Pharmacol. Ther.* **5**, 673

La Roche M & Brodie B B (1960) *J. Pharmacol. exp. Ther.* **130**, 134

Modell W (1964) *Clin. Pharmacol. Ther.* **5**, 265

Prescribers Journal (1965) **4**, 96

Strong F M (1962) *Amer. J. Clin. Nut.* **11**, 500

West G B (1964) *J. Pharm. Pharmacol.* **16**, 788

Wilson G M (1962) In: Symposium on Clinical Trials. Pharmaceutical Society of Great Britain. London; p 53

Displacement of One Drug by Another from Carrier or Receptor Sites

by Bernard B Brodie PhD
(Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda, Maryland, USA)

Abstract

The medium of drug transfer is the water of plasma and extracellular fluid. Without complicating factors, the level of drug at a receptor site would be equal to that in the tissues and in plasma, and in dynamic equilibrium. Actually, almost all drugs are reversibly bound to proteins in plasma or tissue. The bound drug, often a high proportion of the total, acts as a reservoir, preventing wild fluctuations between ineffective and toxic levels of the biologically active unbound fraction.

Displacement from a receptor site diminishes drug activity, but displacement from plasma or tissue proteins augments the effect by making more unbound drug available at the receptor site.

Atropine has no intrinsic activity, but displaces acetylcholine or pilocarpine from receptors at parasympathetic nerve endings. Similarly guanethidine competes with noradrenaline at sympathetic nerve endings, but in turn is displaced by amphetamine-like drugs.

Many acidic drugs (phenylbutazone, sulfonamides, coumarin anticoagulants, salicylates, &c.) are highly bound to one or two sites on albumin molecules. When the limited carrying capacity of the plasma proteins is filled, any unbound surplus is usually soon metabolized or excreted, so the plasma level becomes restabilized. Meanwhile, however, there may be dramatic effects such as hypoglycemia, when sulfonamides are given to patients on tolbutamide, or bleeding when phenylbutazone is given to patients on warfarin.

Although hormones, like thyroxine, insulin and cortisol, are carried by specific proteins, they too can be displaced. All the antirheumatic drugs so far examined have displaced cortisol and presumably driven it into tissues. This may be one mechanism of action. Possibly the sulfonylurea drugs act by displacing insulin from proteins in the pancreas, plasma or elsewhere.

In 1924 Storm van Leeuwen wrote:

> 'It may be assumed that every drug, before acting must be absorbed by dominant receptors, present at the sites of action of the drug. The question rises as to what happens when two drugs are introduced in the body at the same time. If the two drugs have the same dominant receptors, it is very likely that one drug will be more easily absorbed than the other. The second drug may be replaced by the first one and by this procedure the action of the second drug may be antagonized. . . . replacement of one drug by another on