Clin. Pharmacokinet. 21 (3): 195-212, 1991
0312-5963/91/0009-0195/$09.00/0

CPK1 056

Omeprazole Drug Interaction Studies

Tommy Andersson
Department of Clinical Pharmacology, Hässle Research Laboratories,
Mölndal, Sweden

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Summary

This review examines the literature on drug interactions with omeprazole. Different mechanisms have been proposed as potential causes for such interactions. First, the absorption of some drugs might be altered due to the decreased intragastric acidity resulting from omeprazole treatment. There was no effect of omeprazole on the absorption of amoxycillin, bacampicillin and alcohol, while the amount of digoxin and nifedipine absorbed was increased by 10 and 21%, respectively, both increases probably being of no clinical significance. Secondly, the metabolism of high clearance drugs might be altered by changes in liver blood flow, although that is not affected by omeprazole, as indicated by the unchanged elimination of indocyanine green. In addition, the clearance of intravenously administered lidocaine (lignocaine) [a high clearance drug] was unaffected by omeprazole, further indicating that the latter does not alter liver blood flow. Thirdly, since omeprazole is a substituted benzimidazole, it might have the potential to interfere

with the metabolism of other drugs by altering the activity of drug metabolising enzymes in the cytochrome P450 system, through either induction or inhibition. There is no indication of induction of this enzyme system in any interaction study with omeprazole. As regards inhibition, on the other hand, there is now considerable information available which indicates that omeprazole has the potential to partly inhibit the metabolism of drugs metabolised to a great extent by the cytochrome P450 enzyme subfamily IIC (diazepam, phenytoin), but not of those metabolised by subfamilies IA (caffeine, theophylline), IID (metoprolol, propranolol) and IIIA (cyclosporin, lidocaine, quinidine). Since relatively few drugs are metabolised mainly by IIC compared with IID and IIIA, the potential for omeprazole to interfere with the metabolism of other drugs appears to be limited.

Omeprazole, a substituted benzimidazole, has been shown to suppress gastric acid secretion by inhibiting H^+, K^+-ATPase in the parietal cell (Fellenius et al. 1981; Lindberg et al. 1986). The degree of suppression of gastric acid secretion is correlated with the area under the plasma omeprazole concentration-time curve (AUC), and is not directly related to the plasma concentration of the drug at any given time (Lind et al. 1983). Despite the fact that omeprazole is rapidly eliminated from plasma, some antisecretory effect is still present 24 to 72h after a dose. The long duration of action is due to the prolonged binding of the active form of the drug to the H^+, K^+-ATPase in the parietal cells (Brändström et al. 1989). Results from studies on the healing of peptic ulcers and erosive reflux oesophagitis have shown that omeprazole 20 or 40mg once daily heals these acid-related diseases significantly more rapidly than histamine H_2-receptor antagonists (Bardhan et al. 1986; Hetzel et al. 1988; Klinkenberg-Knol et al. 1987; Walan et al. 1989).

The plasma elimination half-life ($t_{1/2\beta}$) of omeprazole is usually shorter than 1h, although a few individuals exhibit slower elimination ($t_{1/2\beta} \approx 2$h) [Andersson et al. 1990b]. These individuals have recently been shown to be poor hydroxylators of *S*-mephenytoin (Andersson et al. 1990d), which suggests that a major part of omeprazole metabolism is mediated via *S*-mephenytoin hydroxylase, an enzyme within the cytochrome P450 system. Omeprazole is completely metabolised and its average plasma clearance is 30 L/h. The main metabolites found in plasma are hydroxy-omeprazole and omeprazole sulphone, neither of which contributes to the antisecretory effect (Wallmark, unpublished results). Almost 80% of a given oral or intravenous dose is excreted as metabolites in urine (Regårdh et al. 1990); the remainder is found in faeces (Regårdh et al. 1990), primarily originating from bile secretion (Lind et al. 1987).

The pharmacokinetics of unchanged omeprazole are unaltered in patients with renal failure, but the renal excretion of the metabolites is impaired (Naesdal et al. 1986); this decrease, however, appears to be compensated by an increased capacity in alternative routes of elimination, primarily biliary secretion. Patients with liver cirrhosis display an impaired metabolism of omeprazole (Andersson et al. 1986), resulting in a $t_{1/2\beta}$ of approximately 3h. Elderly healthy people may have an age-related decrease in hepatic blood flow leading to impaired liver clearance of preferably high clearance drugs (Skaunic et al. 1978; Wynne et al. 1990); accordingly, the rate of metabolism of omeprazole (which is a medium clearance drug) is somewhat decreased in the elderly (Cederberg et al. 1989).

As might be expected, the pharmacokinetics of omeprazole in patients with duodenal ulcer do not differ from those in healthy volunteers of comparable age (Naesdal et al. 1984; Sharma et al. 1984).

More than 11 million patient treatments with omeprazole have been presented to date (April 1991). This widespread use inevitably means that a large number of patients will be taking other medication concurrently, and thus it is important to be aware of any clinically relevant drug-drug interactions between omeprazole and other drugs frequently combined with it. The interaction spec-

trum for cimetidine (an H_2-receptor antagonist) is considerable, while that of another H_2-receptor antagonist, ranitidine, is less pronounced (Sax et al. 1988). In general, the safety record of omeprazole has been favourable (Sölvell 1989), but the question still remains whether this agent could alter the plasma concentrations, and hence the effect, of other drugs given concomitantly. This review discusses some potential mechanisms which may cause interactions and the results from the large number of interaction studies between omeprazole (administered as enteric coated granules) and other drugs that have been judged of clinical relevance.

1. Mechanisms of Potential Drug Interactions with Omeprazole

1.1 Absorption

Omeprazole exerts its effect by inhibiting the secretion of gastric acid. Following therapeutic doses, intragastric pH may be elevated from untreated values of 1 to 2 to values of around 3 to 5. This might potentially influence the absorption of acidic drugs, since their ionisation within the stomach should be more pronounced (which prevents passive diffusion). However, Ekenved et al. (1975) demonstrated that aspirin was as completely and rapidly absorbed from a buffered solution as from an unbuffered solution, indicating that a higher gastric pH would not decrease the absorption of this acidic drug. Nonetheless, to overcome hydrolysis within the normally acidic stomach a number of antibiotics such as penicillins and tetracyclines, as well as some drugs that produce gastric irritation, are formulated as enteric-coated tablets or esters (Mayersohn 1979). Since the disintegration and dissolution of some of these drugs is pH dependent they may dissolve in the stomach, due to the elevated pH obtained with omeprazole. However, studies with the acid secretion inhibitors cimetidine and ranitidine have shown scarcely any systematic and clinically significant effects on the absorption of such drugs (Mitchard et al. 1987; Smith & Kendall 1988). The effect of omeprazole on the absorption of some drugs is discussed in section 2.

1.2 Liver Blood Flow

All drugs administered orally must pass through the liver. Hence, liver enzyme activity will be the primary determinant of the systemic availability of hepatically eliminated drugs. Some drugs, for instance lidocaine (lignocaine), are so avidly extracted by the liver, however, that after intravenous administration it is probably their rate of delivery (i.e. the rate of liver blood flow) that primarily determines hepatic clearance.

Histamine causes vasodilatation and hence increases the blood flow in the intestinal circulation, specifically in the superior mesenteric, left gastric and common hepatic arteries (Charbon et al. 1980; Pawlik et al. 1977).Treatment with H_2-receptor antagonists such as cimetidine and ranitidine in theory may counteract such an effect and cause a decreased hepatic blood flow, affecting the clearance of intravenously administered high clearance drugs. However, conflicting results have been obtained with these 2 drugs as regards the effect on liver blood flow. Omeprazole, having no effect on H_2-receptors, would not be expected to have such effects; even so, a study of its influence on the elimination of indocyanine green, which is believed to mirror liver blood flow, has been conducted (section 3). The effect on the disposition of the high clearance drug lidocaine, administered intravenously, might also be considered as an indicator of influence on hepatic blood flow if metabolic activity is unaffected.

1.3 Metabolic Activity

The metabolic activity of cytochrome P450 enzymes (further discussed in section 6) can be altered in 2 ways: it can be either increased by induction or decreased by inhibition.

Structurally, omeprazole is a substituted benzimidazole and as such might be surmised to have the potential to interfere with the hepatic drug metabolism within the cytochrome P450 as indicated by Dickins and Bridges (1982). It has been shown to be completely metabolised by cytochrome P450, and consequently will bind to this enzyme system.

Therefore, the potential for omeprazole to act as a competitive inhibitor of reactions performed by cytochrome 450 was explored. First, interaction studies were performed with 2 nonselective (i.e. metabolised by several enzymes within cytochrome P450) markers for metabolic activity, aminophenazone (aminopyrine) and phenazone (antipyrine), followed by interaction studies with several drugs of clinical interest (sections 4 and 5).

2. *Omeprazole and Absorption of Other Drugs* (table I)

2.1 Amoxycillin and Bacampicillin

The absorption of ampicillin esters has been reported to decrease when gastric acidity is inhibited due to hydrolysis of the esters or by lowered solubility at a higher pH (Sjövall 1985). No such information is available on the hydroxylated derivative amoxycillin. Eight fasting volunteers randomly received bacampicillin 800mg or amoxycillin 1000mg on 4 study days, separated by at least 1 week, in a crossover study (Paulsen et al. 1989). Each ampicillin derivative was administered as a single drug and after 1 week's pretreatment with omeprazole 20mg every morning. Bacampicillin was absorbed more rapidly than amoxycillin and peak serum concentrations (C_{max}) were higher. After omeprazole, the time to reach C_{max} (t_{max}) of both antibiotics appeared to be slightly delayed and the C_{max} of bacampicillin was significantly reduced. Nevertheless, both the AUC and $t_{1/2\beta}$ were unaffected by omeprazole. Thus, it appears that omeprazole does not significantly alter the bioavailability of either amoxycillin or bacampicillin.

2.2 Digoxin

The absorption of this cardiac glycoside was studied in 10 fasting volunteers on 2 occasions, separated by 2 weeks, in a randomised crossover fashion (Oosterhuis & Jonkman 1989) [fig. 1]. Digoxin 1mg was administered either alone or after 1 week's pretreatment with omeprazole 20mg every morning. The AUC of digoxin was increased by 10% following omeprazole treatment, while its $t_{1/2\beta}$ was unchanged. The increased AUC was suggested to be due to increased absorption, resulting from decreased hydrolysis of digoxin within the stomach as a consequence of the elevated pH obtained by omeprazole (Gault et al. 1980). The increase in AUC was regarded by the investigators as having no clinical significance.

2.3 Alcohol

Interactions between drugs and alcohol may have social and medicolegal consequences. The effect of omeprazole 20mg every morning for 1 week on the pharmacokinetics of alcohol 0.8 g/kg was studied in 12 fasting volunteers in a randomised, blind, crossover study (Jönsson et al. 1990) [fig. 2].

Table I. Influence of oral omeprazole on the absorption of single doses of other drugs in healthy volunteers

Drug	Dose (mg)	Omeprazole dose (mg/day × days)	Change (%)		Reference
			AUC	$t_{1/2\beta}$	
Alcohol	0.8 g/kg	20 × 7	NC	NC	Jönsson et al. (1990)
Amoxycillin	1000	20 × 7	NC	NC	Paulsen et al. (1989)
Bacampicillin	800	20 × 7	NC	NC	Paulsen et al. (1989)
Digoxin	1	20 × 8	+10	NC	Oosterhuis & Jonkman (1989)
Nifedipine	10	20 × 1[a]	NC	NC	Danhof et al. (1989)
	10	20 × 7[b]	+21	NC	Danhof et al. (1989)

a Median intragastric pH of 1.5 during absorption.

b Median intragastric pH of 3.8 during absorption.

Abbreviations: AUC = area under the plasma concentration-time curve; $t_{1/2\beta}$ = elimination half-life; NC = no significant change.

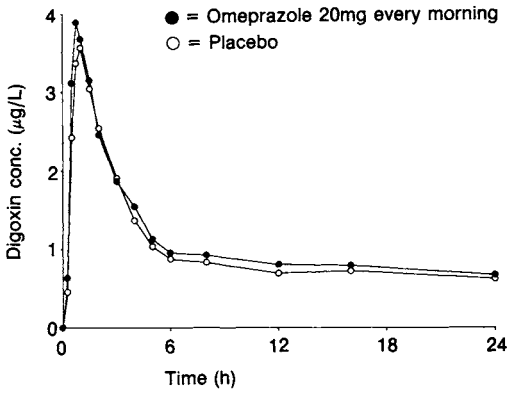

Fig. 1. Mean plasma digoxin concentrations following administration of digoxin 1mg during treatment with omeprazole and placebo in 10 volunteers (data from Oosterhuis & Jonkman 1989, with permission).

The mean values of the blood C_{max}, t_{max}, the apparent volume of distribution (Vd), the elimination rate from blood and the AUC of alcohol were all unchanged following omeprazole pretreatment, compared with placebo. From these results it was concluded that omeprazole did not affect the absorption, distribution or elimination of alcohol after bolus oral administration yielding blood alcohol concentrations within the social drinking range.

2.4 Nifedipine

The effect of single doses of omeprazole 20mg and repeated administration of the same dose every morning for 1 week on the pharmacokinetics and effects of nifedipine 10mg (in capsules) was studied in 10 fasting volunteers in a randomised, double-blind, crossover, placebo-controlled study (Danhof et al. 1989). The AUC of nifedipine was similar to the control value following a single dose of omeprazole, while it was increased by 21% after the week's pretreatment; the $t_{1/2\beta}$ was unchanged in both experiments. Assuming that the Vd of nifedipine was also unchanged, the increase in AUC following repeated doses of omeprazole could be due either to a decreased first-pass elimination or an increased absorption as a consequence of the elevated pH obtained (median pH values 3.8 versus 1.3). If inhibition of the first-pass elimination was the cause, an increased AUC would probably also have been obtained after a single dose of omeprazole. Moreover, the pH was not elevated compared with the control in the single-dose experiment. Thus, the most likely explanation for the effect on nifedipine observed following repeated omeprazole administration is an increased absorption due to the elevated pH compared with the control and single-dose experiments. Support for this hypothesis was obtained in an interaction study with the acid secretion inhibitor ranitidine and nifedipine (Adams et al. 1986). Concomitant administration of these 2 drugs resulted in a significantly increased AUC of nifedipine, while the addition of 200ml of 0.1 mol/L HCl abolished this effect of ranitidine. The increase in AUC of nifedipine following omeprazole was judged by the investigators to have no clinical significance.

3. Omeprazole and Liver Blood Flow

Indocyanine green elimination was measured in 12 fasting volunteers in a randomised crossover study by Mertz Nielsen et al. (1986). Ten minutes after an intravenous dose of omeprazole 0.5 mg/kg or placebo (0.9% NaCl), indocyanine green 12.5mg was given as a bolus injection and the

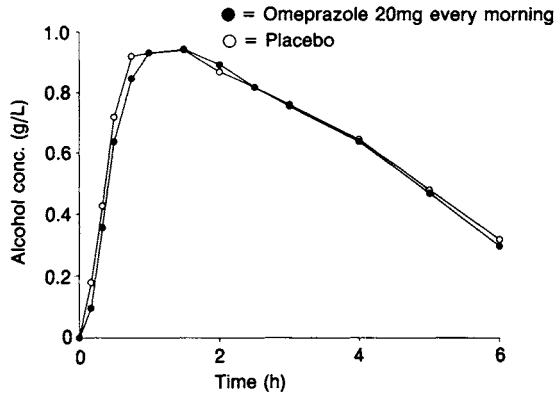

Fig. 2. Mean blood alcohol concentrations following administration of alcohol 0.8 g/kg during treatment with omeprazole and placebo in 12 volunteers (data from Jönsson et al. 1990, with permission).

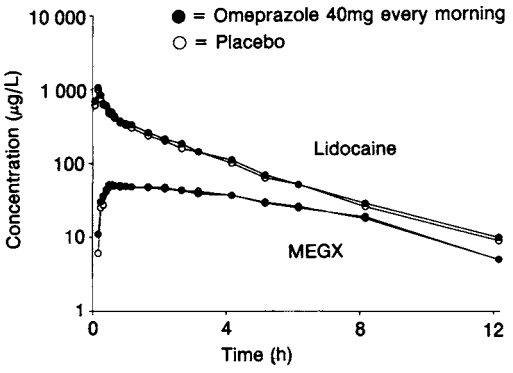

Fig. 3. Mean plasma concentrations of lidocaine (lignocaine) and its major metabolite monoethylglycinexylidide (MEGX) following lidocaine 1 mg/kg intravenously during treatment with omeprazole and placebo in 10 volunteers (data from Bannister et al. 1990, with permission).

plasma concentrations of indocyanine green were measured for 12 min thereafter. The elimination rate of indocyanine green following omeprazole was similar to that after placebo, indicating that hepatic blood flow is unchanged by omeprazole.

3.1 Lidocaine

Further support for the conclusion that omeprazole does not affect hepatic blood flow is obtained in an interaction study with the high clearance drug lidocaine (Bannister et al. 1990) [fig. 3]. In this randomised, double-blind, crossover study, 10 fasting volunteers received lidocaine intravenously on 2 occasions separated by 2 weeks and after 8 days' pretreatment with either omeprazole 40mg every morning or placebo. Cardiovascular variables and electrocardiograph (ECG) pattern, as well as the pharmacokinetic parameters of lidocaine (clearance, Vd, $t_{1/2\beta}$) and its active metabolite monoethylglycinexylidide (MEGX), were unaltered by omeprazole pretreatment. The investigators concluded that omeprazole does not alter hepatic blood flow and does not influence the metabolism of either lidocaine or MEGX.

4. Omeprazole and Markers of Metabolic Status

Aminophenazone and phenazone have been used as model drugs to investigate alterations in drug metabolism caused by physiological, pharmacological and environmental factors (Vessel 1979). The first is oxidatively demethylated, probably as a nonselective substrate for cytochrome P450; the second is principally hydroxylated, and at least 3 metabolites are produced by processes which probably involve 3 different cytochrome P450 enzymes.

4.1 Aminophenazone and Phenazone

Ten volunteers received [^{14}C]aminophenazone (1.5 μCi) intravenously and phenazone 1g orally before and after 2 weeks' pretreatment with omeprazole 60mg every morning, and 9 volunteers (6 of whom also participated in the 60mg study) were enrolled in corresponding investigations after 2 weeks' pretreatment with omeprazole 30mg every morning (Henry et al. 1984). In the study with the high daily omeprazole dose, the $t_{1/2\beta}$ of aminophenazone determined from $^{14}CO_2$ was prolonged by 21%, and the amount of the dose demethylated in 2h was decreased by 19%. Phenazone $t_{1/2\beta}$ was prolonged by 10%, while the decrease in mean clearance (14%) was not statistically significant. In the low dose (30mg) study, the small changes observed for aminophenazone were not statistically significant and the values for phenazone were identical to control values.

From these results it might be suggested that omeprazole has the potential to interfere with the metabolism of other drugs which are mainly metabolised by cytochrome P450 enzymes. It should be remembered, however, that the effect on these 2 drugs was very modest and obtained only with high doses of omeprazole. Nevertheless, it is worth discussing the reliability in the results obtained for an acid secretion inhibitor like omeprazole as regards the effect on the 'metabolic activity' of these model drugs. Being weak bases, aminophenazone and phenazone are taken up from the blood by the

acidic parietal cells and secreted into the stomach. Both drugs are also subject to passive diffusion into the acidic milieu of the stomach. The rate at which they are cleared into the gastric lumen depends on mucosal blood flow and parietal cell function (Muller-Lissner et al. 1981) as well as on intragastric pH. Hence, omeprazole treatment could result in the inhibition of both gastric secretion and passive diffusion of aminophenazone and phenazone, which would reduce the fraction reabsorbed from the intestine and subsequently metabolised. Therefore, the somewhat decreased 'metabolic activity' observed following omeprazole treatment might instead reflect an altered partition of these agents into the gastric lumen.

Nevertheless, it was thought to be advisable to further evaluate possible interactions with therapeutically important drugs, especially those extensively metabolised by cytochrome P450 and possessing a narrow therapeutic index.

5. Omeprazole and Metabolism of Other Drugs (table II)

The metabolism of alcohol and nifedipine was unaffected by omeprazole, as discussed in sections 2.3 and 2.4, respectively.

5.1 Antiarrhythmics

5.1.1 Lidocaine

Lidocaine is discussed above (section 3.1), and the lack of effect on the disposition of this drug and its metabolite indicates that its metabolism is unaffected by treatment with omeprazole 40mg once daily in the morning.

5.1.2 Quinidine

The effect of omeprazole 40mg every morning on the pharmacokinetics and pharmacodynamics of quinidine and its major metabolite 3-hydroxyquinidine was studied in 8 fasting volunteers by Ching et al. (1990). In this randomised, double-blind, crossover study, quinidine 400mg was administered orally on 2 occasions, after 1 week's pretreatment with omeprazole or with placebo. Both the ECG pattern (QT interval) and the pharmacokinetic parameters of quinidine and its active metabolite were unaltered by omeprazole pretreatment. Since quinidine is a medium clearance drug, any alteration in the activity of the enzymes responsible for its metabolism should have been detected in this study.

5.2 Xanthine Derivatives

5.2.1 Theophylline

The effect of omeprazole on the metabolism of the bronchodilator theophylline has been investigated in 3 different studies, none of which showed any interaction. In 1 study omeprazole 40mg every morning for 1 week did not influence the plasma clearance of a single intravenous dose of theophylline 200mg given to 8 fasting volunteers (Gugler & Jensen 1987) [fig. 4a]. The pharmacokinetics of an oral dose of theophylline 160mg were also unaltered by omeprazole in these subjects (Gugler, unpublished results) [fig. 4a].

Steady-state oral theophylline clearance was determined in a randomised, double-blind, crossover study in which 8 volunteers received theophylline 2.5 mg/kg twice daily for 1 week together with either omeprazole 20mg every morning or placebo, separated by a 1-week washout period (Genève et al. 1991). The plasma clearance of theophylline and the renal excretion of 3 different metabolites, 1 hydroxylated and 2 demethylated, were similar during both periods, leading to the conclusion that omeprazole has no effect on the steady-state metabolism of theophylline. In the third study, the short term effect of intravenous omeprazole 40 and 80mg on the metabolism of a single dose of intravenous theophylline 400mg was investigated in 8 fasting volunteers (Oosterhuis & Jonkman 1989) [fig. 4b]. In accordance with the results of the other 2 studies, omeprazole did not influence the metabolism of the relatively high dose of theophylline given in this investigation.

5.2.2 Caffeine

To investigate the possible influence of repeated omeprazole administration on the metabolism of caffeine, which has been shown to reflect the ac-

Table II. Influence of oral omeprazole on the metabolism of other drugs. All studies are in healthy volunteers, unless otherwise stated

Drug	Dose (mg)	Route	Omeprazole dose (mg/day × days)	Change (%)					Reference
				CL	Vd	$t_{1/2\beta}$	AUC	C^{ss}	
Lidocaine (lignocaine)	1/kg	IV	40 × 8	NC	NC				Bannister et al. (1990)
Quinidine	400	PO	40 × 7			NC	NC		Ching et al. (1990)
Theophylline	200	IV	40 × 7	NC	NC				Gugler & Jensen (1987)
	160	PO	40 × 7			NC	NC		Gugler (unpublished data)
	2.5/kg bid[b]	PO	20 × 7	NC[a]					Genève et al. (1991)
	400	IV	40/80[h]	NC					Oosterhuis & Jonkman (1989)
Warfarin-*S*	4.7[c]	PO	20 × 14					NC	Sutfin et al. (1989)
-*R*								+12	
Diazepam	0.1/kg	IV	40 × 7	−54	NC				Gugler & Jensen (1985)
	0.1/kg	IV	20 × 7	−27	NC				Andersson et al. (1990a)
	0.1/kg[d]	IV	20 × 7	−26	NC				Andersson et al. (1990b)
Phenytoin	250	IV	40 × 7	−15	NC				Gugler & Jensen (1985)
	300	PO	40 × 7			NC	+19		Prichard et al. (1987)
	300[e]	PO	20 × 21					NC	Andersson et al. (1990c)
Metoprolol	100[b]	PO	40 × 8				NC	NC	Andersson et al. (1991b)
Propranolol	80 bid [b]	PO	20 × 8				NC	NC	Henry et al. (1987)
Cyclosporin	250[f]	PO	20 × 14					NC	Blohmé et al. (1991)
Caffeine	–[g]	PO	20 × 7	NC					Andersson et al. (1991a)

a Oral clearance.
b For 1 week.
c For 2 weeks.
d No interaction in slow metabolisers.
e For 3 weeks in patients.
f For 2 weeks in patients.
g 2-3 cups of coffee.
h Intravenous administration

Abbreviations: IV = intravenous administration; PO = oral administration; CL = plasma clearance; Vd = volume of distribution; $t_{1/2\beta}$ = elimination half-life; AUC = area under the plasma concentration-time curve; C^{ss} = concentration at steady-state; NC = no significant change.

tivity of 1 specific enzyme within the hepatic cytochrome P450 family (P450IA2; Grant et al. 1987; Sesardic et al. 1990), 10 healthy nonsmoking male volunteers received omeprazole 20mg every morning or placebo, each for 1 week, in a randomised, double-blind, crossover manner (Andersson et al. 1991a). The 2 treatments were given 2 to 3 weeks apart. Coffee intake was standardised on study days, the sixth and seventh days of each period, when urine was collected twice daily and urinary metabolites of caffeine were determined. The urinary metabolite ratio of 3 paraxanthine 7-demethylation products relative to a paraxanthine hydroxylation product correlates to caffeine clearance and hence P450IA2 activity (Campbell et al. 1987). The calculated ratio was 4.8 (3.9 to 5.6, 95% confidence interval) and 4.6 (3.6 to 5.5, 95% confidence interval) in the placebo and omeprazole periods, respectively. These results show that the metabolism of caffeine was unaltered following omeprazole

treatment, demonstrating that omeprazole has no influence on cytochrome P450IA2 activity in the clinical situation. Furthermore, the activity of 2 other enzymes – xanthine oxidase and *N*-acetyl transferase – also appeared to be unaltered following omeprazole administration.

5.3 Warfarin

The effect of concomitant treatment with omeprazole 20mg every morning on the plasma concentration and anticoagulation effect of warfarin was studied in 21 healthy volunteers (Sutfin et al. 1989). An initial 3 weeks' treatment with warfarin alone was administered to determine the dosages required for the subjects' vitamin K–dependent coagulation factors to fall within 10 to 20% of the normal range, as determined by the 'Trombotest'. Omeprazole or placebo were then administered concomitantly with warfarin for 2 weeks in a double-blind, randomised, crossover fashion and 'Trombotest' values were measured daily on weekdays throughout the crossover period. Omeprazole had no effect on the mean plasma *S*-warfarin concentration but caused a slight (12%) increase in that of the *R*-isomer. The 'Trombotest' values exhibited large inter- and intrasubject variability during both omeprazole and placebo treatment; however, there was a small but statistically significant decrease in the mean value from 21.1% without to 18.7% with omeprazole (95% confidence interval for difference of means: −4.6, −0.1). Those volunteers with 'Trombotest' values nearest the therapeutic range (5 to 15%) exhibited less change during omeprazole treatment, and no changes occurred that required a change in warfarin dosage. The interaction of omeprazole with warfarin might be due to a stereoselective inhibition of the hepatic metabolism of the less potent *R*-warfarin enantiomer. The small effect of omeprazole on the anticoagulation activity of warfarin is not likely to be of clinical importance, according to the investigator. Results from a study in warfarin-anticoagulated patients with 3 weeks of concomitant treatment with omeprazole 20mg indicate that omeprazole does not interfere significantly with warfarin metabolism in these patients (Unge, personal communication).

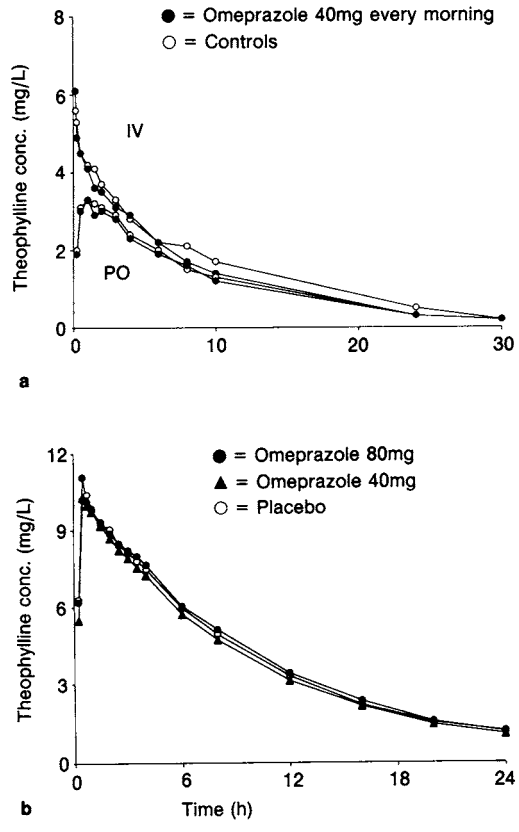

Fig. 4. Mean plasma theophylline concentrations following (**a**) oral (unpublished data) and intravenous theophylline 160 and 200mg, respectively, during treatment with omeprazole compared with baseline, in 8 volunteers; (**b**) intravenous theophylline 400mg after placebo and intravenous omeprazole in 8 volunteers. Note different scales on *x*-axes (data from Gugler & Jensen 1987 and Oosterhuis & Jonkman 1989, with permission).

5.4 Anticonvulsants/Sedatives

5.4.1 Diazepam

The effect of omeprazole on the pharmacokinetics of the benzodiazepine diazepam has been investigated in 3 different studies, all of which showed an interaction. Omeprazole 40mg every morning for 1 week in 8 fasting volunteers resulted in a 54% decrease in the plasma clearance of intravenously administered diazepam 0.1 mg/kg (Gugler & Jensen 1985); protein binding and Vd were unaltered. In a randomised, double-blind, crossover, placebo-

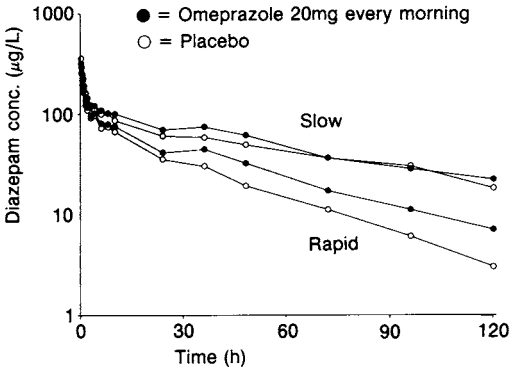

Fig. 5. Mean plasma concentrations of diazepam in 4 slow and 6 rapid metabolisers of omeprazole following intravenous diazepam 0.1 mg/kg during treatment with omeprazole and placebo (after Andersson et al. 1990b).

controlled study 12 fasting volunteers received the same dose of diazepam as in the previous investigation, but the omeprazole dose was reduced to 20mg every morning (Andersson et al. 1990a). The plasma clearance of diazepam in this study was decreased by 27% (cimetidine 400mg twice daily, used as a reference in the same study, decreased diazepam clearance by 38%).

Since diazepam has a wide therapeutic range, it is unlikely that concomitant treatment with therapeutically recommended doses of omeprazole will result in a clinically significant interaction. However, since the inhibition of diazepam metabolism appears to be dose dependent, it was especially interesting to compare this interaction between slow metabolisers who exhibit higher plasma omeprazole concentrations and normal, rapid metabolisers of omeprazole. Thus, the effect of omeprazole treatment on plasma diazepam concentrations was studied in 4 slow and 6 rapid metabolisers of omeprazole in a randomised, double-blind, crossover manner (Andersson et al. 1990b) [fig. 5]. Single intravenous doses of diazepam 0.1 mg/kg were administered after 1 week of oral treatment with either omeprazole 20mg every morning or placebo. Blood was collected up to 120h after the diazepam dose (while once-daily omeprazole or placebo administration continued) in order to measure diazepam and its major metabolite, demethyl-diazepam. The results were that slow metabolisers of omeprazole also metabolised diazepam slowly, exhibiting only half the plasma clearance of the others. The mean clearance of diazepam was decreased 26% after omeprazole in the rapid metabolisers, in accordance with the results of the previous study, whereas the slow group showed no apparent interaction. The plasma concentrations of desmethyldiazepam exhibited a slower formation in the slow metabolisers, but seemed to be unaffected by omeprazole treatment. In the rapid metabolisers the formation rate of this metabolite was slightly decreased by omeprazole.

Since a major part of the metabolism of both omeprazole and diazepam is probably mediated by *S*-mephenytoin hydroxylase (Andersson et al. 1990d; Bertilsson et al. 1989), the increase in plasma diazepam concentrations observed during omeprazole treatment in rapid metabolisers is probably the result of partial inhibition of this enzyme. This type of interaction is a well known phenomenon that has been observed for other drugs metabolised by specific enzymes, for instance by debrisoquine hydroxylase, and is usually due to competitive inhibition (Haefeli et al. 1990; Wagner et al. 1987). Slow omeprazole metabolisers, on the other hand, will not display increased plasma diazepam concentrations during repeated doses of omeprazole. In these subjects *S*-mephenytoin hydroxylase is probably functionally altered (Meier & Meyer 1987) and omeprazole and diazepam may be metabolised by other enzymes which are not inhibited by omeprazole in the doses used. Analogous results have been reported for poor metabolisers of debrisoquine, who showed no metabolic impairment of substrates for debrisoquine hydroxylase following administration of known inhibitors of this enzyme (Funck-Brentano et al. 1989; Steiner & Spina 1987).

5.4.2 Phenytoin

The effect of omeprazole on the pharmacokinetics of phenytoin has been studied in healthy volunteers and in patients with epilepsy. Omeprazole 40mg every morning for 1 week administered to 8 fasting volunteers resulted in a 15% decrease in the plasma clearance of intravenously admini-

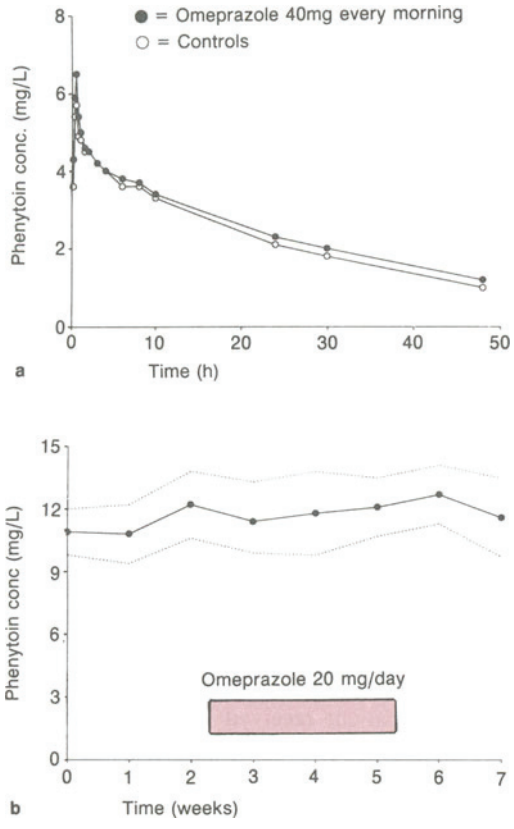

Fig. 6. (**a**) Mean plasma phenytoin concentrations following intravenous phenytoin 250mg during treatment with omeprazole compared with pretreatment control, in 8 volunteers; (**b**) steady-state plasma phenytoin concentrations (mean ± SE) in 8 patients with epilepsy receiving phenytoin 300 mg/day during treatment with omeprazole 20mg every morning for 3 weeks. Note different scales on *x*-axes (after Gugler & Jensen 1985 and Andersson et al. 1990c).

stered phenytoin 250mg (Gugler & Jensen 1985) [fig. 6a]. Protein binding and Vd were unaltered. In a randomised, double-blind, crossover study by Prichard et al. (1987), 10 fasting volunteers received either omeprazole 40mg every morning or placebo for 9 days, a single oral dose of phenytoin 300mg being administered on the seventh day. The AUC of phenytoin was increased by 19% while the $t_{1/2\beta}$ was not significantly changed during omeprazole treatment.

To evaluate this effect clinically, the influence of omeprazole on the steady-state phenytoin concentrations in 8 epileptic patients was investigated by Andersson et al. (1990c) [fig. 6b]. The concentrations were measured once a week before, during and after 3 weeks of concomitant omeprazole 20mg every morning; urinary excretion of phenytoin and its metabolite [5-(*p*-hydroxyphenyl)-5-phenylhydantoin] was determined before and at the end of the omeprazole treatment period. The dosage of phenytoin (mean 300 mg/day) was not changed in any patient during the study. Measured values showed no change during omeprazole treatment. The results from this study suggest that concomitant omeprazole treatment in dosages likely to be used for peptic ulcer (20 mg/day) will not significantly affect the steady-state plasma concentrations of phenytoin in patients with epilepsy.

5.5 β-Blockers

5.5.1 Metoprolol

In a randomised, double-blind, crossover study, 7 healthy volunteers were concomitantly administered metoprolol 100mg every morning and omeprazole 40mg every morning or placebo, for 8 days (Andersson et al. 1991b) [fig. 7a]. Plasma concentrations of the *R*- and *S*-enantiomers of metoprolol were determined on the eighth day of each treatment. The volunteers were also characterised by their metabolic capacity to hydroxylate debrisoquine, all being extensive metabolisers of metoprolol. Concomitant omeprazole treatment had no significant influence on the steady-state plasma concentrations of the 2 enantiomers of metoprolol. Moreover, the individual's capacity to metabolise omeprazole appears to have no influence on the plasma concentration of metoprolol as judged from trials in 1 subject who was a slow metaboliser of omeprazole and hence exhibited significantly higher than average plasma omeprazole concentrations.

5.5.2 Propranolol

Eight healthy volunteers in a randomised, double-blind crossover study received oral propranolol 80mg twice daily with omeprazole 20mg

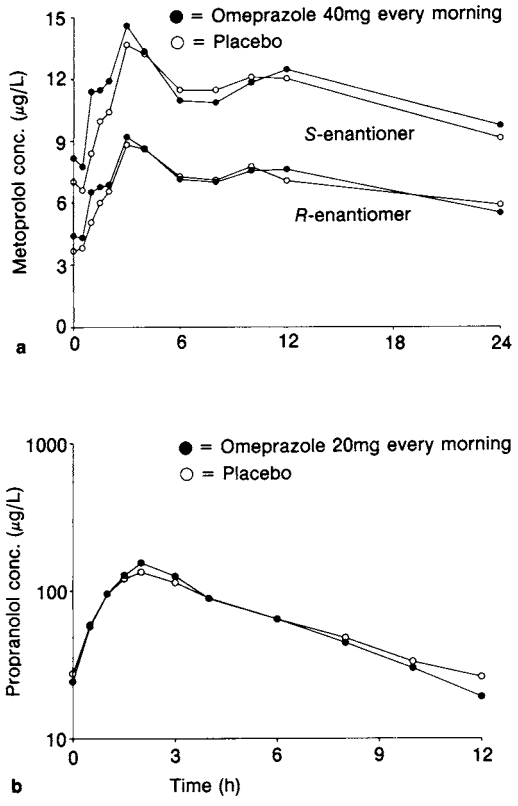

Fig. 7. Mean steady-state plasma concentrations of (**a**) *R*- and *S*-enantiomers of metoprolol following oral administration of metoprolol 100mg every morning during treatment with omeprazole or placebo in 7 volunteers; (**b**) propranolol following oral administration of propranolol 80mg twice daily during treatment with omeprazole or placebo in 8 volunteers. Note different scales on *x*-axes (after Andersson et al. 1991b; Henry et al. 1987)

or placebo each morning for 8 days (Henry et al. 1987) [fig. 7b]. Propranolol pharmacokinetics and effect were measured on day 8 of each treatment period. Its AUC and peak and trough steady-state concentrations were unaffected by omeprazole, which also failed to alter its pharmacodynamic effect as assessed by exercise tests on day 8. The authors concluded that omeprazole in the dosage likely to be used for peptic ulcer has no significant effect on the pharmacokinetics or action of propranolol.

5.6 Cyclosporin

Antisecretory drugs are often used in renal transplant patients. Cyclosporin, which is the basis of most modern immunosuppressive protocols, unfortunately has a narrow therapeutic range and is subject to strong interactions with other drugs (Yee & McGuire 1990a,b). In addition to a possible metabolic interaction, H_2-receptor antagonists have been reported to reverse histamine-mediated immunosuppression, which could prove to be deleterious to transplant organs (Badger et al. 1984; Schnaper et al. 1987). To evaluate any potential effect of omeprazole on plasma concentrations of cyclosporin, 10 patients aged between 29 and 51 years with renal transplants 1 to 7 years old were investigated (Blohmé et al. 1991) [fig. 8]. All patients had stabilised renal function and received unchanged immunosuppressive and other medication for several months, with cyclosporin doses ranging between 175 and 350 mg/day. The study was conducted as a randomised, blind, crossover trial. Each patient received omeprazole 20mg or placebo once daily for 2 consecutive weeks. Blood samples to determine trough whole blood concentrations of cyclosporin were obtained twice weekly

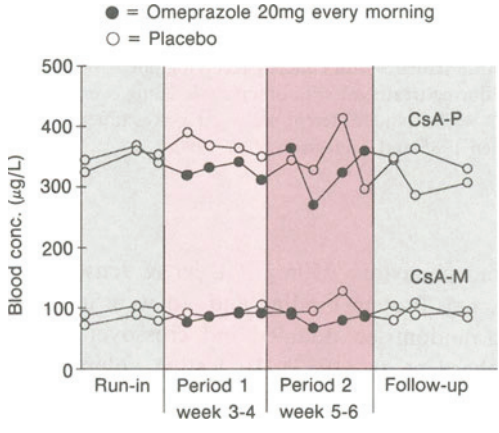

Fig. 8. Mean steady-state blood concentrations of cyclosporin measured by cyclosporin A mono- and polyclonal methods (CsA-M and CsA-P, respectively), in 10 renal transplant patients during treatment with omeprazole and placebo (from Blohmé et al. 1991, with permission).

during the 4 study weeks, as well as 2 weeks before and after. Renal function and other routine laboratory tests were performed once a week. Cyclosporin concentrations, assessed both as the parent compound [Sandoz's monoclonal antibody radioimmunoassay (RIA) test] and together with its metabolites [Abbott's polyclonal enzyme-linked immunoabsorbent assay (ELISA) test], were not significantly changed during omeprazole treatment. It appears that omeprazole does not interfere significantly with cyclosporin metabolism in stabilised renal transplant patients and it may be safely used without extra monitoring of blood cyclosporin concentrations.

6. Cytochrome P450

Cytochrome P450 enzymes are haemoproteins found in different tissues of the body, most abundantly in the liver. They are involved in the oxidative metabolism of several endogenous substances, such as steroids, fatty acids and prostaglandins; many of these enzymes, particularly those found in the liver, also metabolise lipophilic drugs and other xenobiotics. In general, cytochrome P450 enzymes convert lipophilic substrates to more hydrophilic derivatives, which are then more easily excreted from the body via urine or bile, either directly or after conjugation.

Early literature data on the cytochrome P450 enzymes refer almost exclusively to studies in rodents. Lately, however, extensive work has been conducted on human tissue and a considerable amount of information has been gathered regarding different enzymes of the human cytochrome P450, verified in several cases in a clinical situation.

The cytochrome P450 enzymes appear to be derived from a gene superfamily which has undergone divergent evolution, with the ancestral gene probably being more than 2.5 billion years old (Gonzalez 1989). On the basis of amino acid sequence similarity, the cytochrome P450 superfamily can be classified into several families. In humans at least 8 such families have been identified (named with roman numerals) and a varying number of subfamilies are present within each, where greater than 59% amino acid sequence similarity exists (Nebert et al. 1989). This huge number of enzymes have evolved over the past 75 to 800 million years, and its diversification has been suggested to coincide with the emergence of aquatic vertebrates on to land, and the consequent changes in their diets which contained toxic substances found in land vegetation (Nelson & Strobel 1987). It has become quite clear, however, that various species have been, and are, developing their own specialised battery of P450 isozymes, particularly those in family P450II, which is one of the three (I, II and III) mainly involved in the hepatic metabolism of drugs. This most probably relates to the evolution of distinctive dietary habits. Furthermore, the activity of cytochrome P450 enzymes can be inhibited or induced by specific drugs or xenobiotics (Barry & Feely 1990).

It is also important to note that some of the enzymes, mostly within family II, are polymorphically expressed, i.e. some individuals within a normal population exhibit slower metabolism via a specific enzyme than the majority, and this property is genetically determined. The 2 polymorphisms within the cytochrome P450 most extensively studied, and apparently the only 2 which have been verified, are the metabolism of debrisoquine, mediated via enzyme IID6, debrisoquine hydroxylase (Eichelbaum & Gross 1990; Mahgoub et al. 1977), and *S*-mephenytoin which is connected to an enzyme within subfamily IIC, *S*-mephenytoin hydroxylase (Küpfer & Preisig 1984; Wilkinson et al. 1989). Among Caucasians, 3 to 10% of the population are poor metabolisers of debrisoquine and ≈3% are poor *S*-mephenytoin hydroxylators (Guengerich 1989). *S*-mephenytoin hydroxylase has been suggested to be responsible for a major part of the metabolism of omeprazole (Andersson et al. 1990d).

7. Omeprazole and Cytochrome P450: Implications for Drug-Drug Interactions (table III)

The findings presented in this review are highly relevant when evaluated together with the existing data of the metabolism of the drugs in question.

Taken together, this knowledge can be used as an important tool to predict potential interactions between omeprazole and other drugs. A prerequisite, however, is knowledge of the enzyme involved in the major metabolism of the particular drug.

S-Mephenytoin hydroxylase (possibly IIC9), which seems to be inhibited by omeprazole to a degree as indicated in section 5.4, has so far been found to be involved in the metabolism of only a few drugs other than diazepam and omeprazole (Wilkinson et al. 1989). Therefore, the potential for drug-drug interactions with omeprazole via this enzyme relates to a limited number of drugs. Even so, mephobarbital (Küpfer & Branch 1985) and hexobarbital (Knodell et al. 1988) – 2 drugs with limited use today – are known to be metabolised by this enzyme, and accordingly an interaction with them might be surmised. Furthermore, the slight interaction observed between omeprazole 40mg every morning and phenytoin, described previously (Gugler & Jensen 1985; Prichard et al. 1987), can probably also be explained by inhibition of a specific enzyme by omeprazole, since phenytoin has recently been suggested to be metabolised within subfamily IIC by an enzyme very closely related to *S*-mephenytoin hydroxylase (Veronese et al. 1990). Tolbutamide is metabolised by the same enzyme as phenytoin (Relling et al. 1990; Veronese et al. 1990), so that some interaction might be expected with this drug also.

The lack of effect of omeprazole on the metabolism of metoprolol (Andersson et al. 1991b), me-

Table III. Omeprazole and cytochrome P450: implications for drug-drug interactions

	Cytochrome P450				
	I	II			III
	IA IA2	IIC IIC8-10	IID IID6	IIE IIE1	IIIA IIIA3-5
Inhibitor	Cimetidine +	Cimetidine + Omeprazole ±	Cimetidine + Ranitidine ±		Cimetidine + Ranitidine ±
Main inducer	Polycyclic hydrocarbons	Phenobarbital Rifampicin		Alcohol	Glucocorticoids Rifampicin
Substrate	Theophylline (–) Caffeine (–) Phenacetin Paracetamol (acetaminophen)	Diazepam (+) Omeprazole Mephobarbital Hexobarbital Phenytoin (±) Tolbutamide	Metoprolol (–) Propranolol (–) Timolol Bufuralol Propafenone Flecainide Encainide Nortriptyline Desipramine Clomipramine Imipramine Perphenazine Dextromethorphan Codeine *N*-propyl-ajmaline etc.	Alcohol (–) Acetone Halothane *N*-Nitroso-DNA	Lidocaine (–) [lignocaine (–)] Quinidine (–) Cyclosporin (–) Nifedipine[a] Diltiazem Erythromycin Midazolam Triazolam Hydrocortisone Progesterone Testosterone Androstenedione OCP etc.

a Increased absorption with omeprazole.

Key: + = interaction; (+) = interaction with omeprazole; – = no interaction; (–) = no interaction with omeprazole; OCP = oral contraceptive pills.

tabolised by debrisoquine hydroxylase (IID6), suggests that the metabolism of other drugs using this enzyme would not be expected to be influenced by omeprazole. This concept is further supported by the lack of effect of omeprazole on the metabolism of another β-blocker, propranolol (Henry et al. 1987). According to Ward et al. (1989), propranolol is metabolised by both IID6 and *S*-mephenytoin hydroxylase, and the activity of both these enzymes must be simultaneously decreased in order to reduce the rate of metabolism of propranolol. Since *S*-mephenytoin hydroxylase is suggested to be partially inhibited by omeprazole, the results from the study of the interaction between omeprazole and propranolol clearly indicates that IID6 is unaffected by omeprazole. Further drugs that are metabolised to a great extent by IID6, and therefore probably will be unaffected by omeprazole, are other β-blockers such as timolol and bufuralol, antiarrhythmics such as propafenone and flecainide, tricylic antidepressants such as nortriptyline and desipramine, neuroleptics like perphenazine, and several more (Brøsen & Gram 1989; Eichelbaum & Gross 1990; Lennard 1989). However, no interaction studies have yet been performed with any of these drugs and omeprazole.

Interaction studies on omeprazole have also been performed with drugs known to be metabolised by other subfamilies within the cytochrome P450 system. Subfamily IA, or more specifically enzyme IA2, has been suggested to play a major role in the metabolism of theophylline (Robson et al. 1988). Omeprazole 40 or 20mg every morning for 1 week did not influence the clearance of that drug in healthy subjects (Genève et al. 1991; Gugler & Jensen 1987), suggesting that the enzyme IA2 is not affected by omeprazole. However, in a study by Diaz et al. (1990) omeprazole was suggested to be an inducer of this enzyme, both *in vitro* and *'in vivo'*. The *in vitro* part was conducted in primary cultures of human hepatocytes taken from patients with hepatic cancers. The *'in vivo'* results were obtained by measuring the P450IA activity in liver biopsy samples from 5 patients with tumours in the digestive tract, taken 5 days prior to and during operation. In the meantime the patients received omeprazole 20 mg/day for 4 days. The IA2 activity in the biopsies was increased by 1.5 to 4 times. The discrepancy between the results from Diaz's study and those from the studies with theophylline can be explained by several factors: the most important is that Diaz et al. appear to have ignored the importance of controls. The study, therefore, does not evaluate the effects of surgical premedications, anaesthetics and physiological stresses, on the activity of P450IA2. Moreover, caution is required in interpreting the results by Diaz et al., since previous workers have shown a 2-fold variation in the levels of P450IA2 in different regions of the liver (Watkins et al. 1990), and the way the biopsy samples were taken initially (needle biopsy) and at operation (wedge liver biopsy) differed systematically. That the findings by Diaz et al. do not reflect the clinical situation was further verified in an interaction study with caffeine, also metabolised by IA2 (Grant et al. 1987; Sesardic et al. 1990), in which omeprazole had no effect on the metabolism of that drug (Andersson et al. 1991a). Paracetamol (acetaminophen), when given in high doses, and phenacetin are metabolised by IA2 (Raucy et al. 1989; Sesardic et al. 1988). Consequently, their metabolism by this enzyme will probably not be affected by omeprazole treatment. The other enzyme within this subfamily, IA1, is not constitutively expressed in the liver, i.e. there are usually no measurable amounts of this enzyme in normal human livers (Sesardic et al. 1988).

Another subfamily which has been extensively studied is IIIA, consisting of enzymes IIIA3 to IIIA5. Enzyme IIIA4 is believed to possess the major metabolising capacity within this subfamily (Wrighton et al. 1990). The calcium antagonist nifedipine, the antiarrhythmics lidocaine and quinidine, and the immunosuppressive drug cyclosporin are all metabolised by this enzyme (Bargetzi et al. 1989; Gonzalez et al. 1988; Guengerich et al. 1986; Kronbach et al. 1988). The absence of interaction between omeprazole and lidocaine (Bannister et al. 1990), quinidine (Ching et al. 1990) and cyclosporin (Blohmé et al. 1991) suggest that the activity of this enzyme is unaffected by omeprazole. The somewhat increased AUC of nifedipine

obtained following omeprazole treatment (Danhof et al. 1989) is probably a result of increased absorption, due to the elevated intragastric pH obtained (see section 2.4), and is probably not caused by inhibited metabolism. Thus, it is probable that omeprazole will not significantly influence the metabolism of drugs by IIIA4. If this is the case, the metabolism of other calcium antagonists such as diltiazem (Pichard et al. 1990), macrolide antibiotics such as erythromycin (Watkins et al. 1985), benzodiazepines like midazolam and triazolam (Kronbach et al. 1989), steroids such as hydrocortisone (Ged et al. 1989), progesterone, testosterone, androstenedione (Aoyama et al. 1989) and oral contraceptives (Guengerich 1988), etc., will be found to be unaffected by omeprazole.

In addition, the enzyme mainly responsible for the metabolism of alcohol in humans is alcohol dehydrogenase, but a specific enzyme within cytochrome P450 (IIE1) is also involved to some extent (Mezey 1976; Wrighton et al. 1986). Accordingly, these enzymes appear to be unaffected by omeprazole.

In summary, the available data indicate that omeprazole has a narrow range of interactions with cytochrome P450 confined to the limited number of drugs metabolised mainly by subfamily IIC. No significant interference with drugs metabolised within subfamilies IA, IID and IIIA has been detected (Andersson 1991).

References

Adams LJ, Antonow DR, McClain CJ, McAllister R. Effect of ranitidine on bioavailability of nifedipine. Abstract. Gastroenterology 90: 1320, 1986

Andersson T. Pharmacokinetics of omeprazole in man; with special reference to single and repeated administration, drug interactions, and polymorphic metabolism, Thesis, University of Göteborg, Sweden, 1991

Andersson T, Andrén K, Cederberg C, Edvardsson G, Heggelund A, et al. Effect of omeprazole and cimetidine on plasma diazepam levels. European Journal of Clinical Pharmacology 39: 51-54, 1990a

Andersson T, Bergstrand R, Cederberg C, Eriksson S, Lagerström PO, et al. Omeprazole treatment does not affect the metabolism of caffeine, Gastroenterology, in press, 1991a

Andersson T, Cederberg C, Edvardsson G, Heggelund A, Lundborg P. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. Clinical Pharmacology and Therapeutics 47: 79-85, 1990b

Andersson T, Lagerström PO, Unge P. A study of the interaction between omeprazole and phenytoin in epileptic patients. Therapeutic Drug Monitoring 12: 329-333, 1990c

Andersson T, Lundborg P, Regårdh CG. Lack of effect of omeprazole treatment of steady-state plasma levels of metoprolol. European Journal of Clinical Pharmacology 40: 61-65, 1991b

Andersson T, Olsson R, Skånberg I, Heggelund A, Johnsson G, et al. Pharmacokinetics of omeprazole in patients with liver cirrhosis. Abstract no. 600. Acta Pharmacologica et Toxicologica 59 (Suppl. 5): 203, 1986

Andersson T, Regårdh CG, Dahl-Puustinen ML, Bertilsson L. Slow omeprazole metabolisers are also poor S-mephenytoin hydroxylators. Therapeutic Drug Monitoring 12: 415-416, 1990d

Aoyama T, Yamano S, Waxman DJ, Lapenson DP, Meyer UA, et al. Cytochrome P-450 hPCN3, a novel cytochrome P-450IIIA gene product that is differentially expressed in adult human liver. Journal of Biological Chemistry 264: 10388-10395, 1989

Badger AM, Young J, Poste G. Reversal of histamine-mediated immunosuppression by structurally diverse histamine type II (H-2) receptor antagonists. International Journal of Immunopharmacology 6: 467-473, 1984

Bannister J, Noble DW, Lamont M, Scott DB. Lack of effect of omeprazole on the disposition of lignocaine and its active metabolite in healthy subjects. Abstract no. PP1363. Abstracts I, World Congresses of Gastroenterology, Sydney, Australia, 26-31 August, 1990

Bardhan KD, Bianchi Porro G, Bose K, Daly M, Hinchliffe RFC, et al. A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcer. Journal of Clinical Gastroenterology 8: 408-413, 1986

Bargetzi MJ, Aoyama T, Gonzalez FJ, Meyer UA. Lidocaine metabolism in human liver microsomes by cytochrome P450IIIA4. Clinical Pharmacology and Therapeutics 46: 521-527, 1989

Barry M, Feely J. Enzyme induction and inhibition. Pharmacology and Therapeutics 48: 71-94, 1990

Bertilsson L, Henthorn TK, Sanz E, Tybring G, Säwe J, et al. Importance of genetic factors in the regulation of diazepam metabolism: relationship to S-mephenytoin, but not debrisoquine, hydroxylation phenotype. Clinical Pharmacology and Therapeutics 45: 348-355, 1989

Blohmé I, Andersson T, Idström JP. No interaction between omeprazole and cyclosporine. Abstract. Gastroenterology 100: A 721, 1991

Brändström A, Lindberg P, Bergman NÅ, Alminger T, Ankner K, et al. Chemical reactions of omeprazole and omeprazole analogues. Acta Chemica Scandinavica 43: 536-611, 1989

Brøsen K, Gram LF. Clinical significance of the sparteine/debrisoquine oxidation polymorphism. European Journal of Clinical Pharmacology 36: 537-547, 1989

Campbell ME, Spielberg SP, Kalow W. A urinary metabolite ratio that reflects systemic caffeine clearance. Clinical Pharmacology and Therapeutics 42: 157-165, 1987

Cederberg C, Andersson T, Skånberg I. Omeprazole: pharmacokinetics and metabolism in man. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 33-40, 1989

Charbon GA, Brouwers HAA, Sala A. Histamine H_1- and H_2-receptors in the gastrointestinal circulation. Naunyn-Schmiedeberg's Archives of Pharmacology 312: 123-129, 1980

Ching MS, Elliott SL, Murdoch RT, Stead CK, Devenish-Meares SE, et al. Quinidine and 3-hydroxy quinidine pharmacokinetics and pharmaco-dynamics are unaltered by omeprazole. Abstract no. PD1157. Abstracts II, World Congresses of Gastroenterology, Sydney, Australia, 26-31 August, 1990

Danhof M, Soons PA, van den Berg G, van Brummelen P, Jansen JBMJ, et al. Interactions between nifedipine and omeprazole. Abstract no. PP11.01. European Journal of Clinical Pharmacology 36 (Suppl.): A258, 1989

Diaz D, Fabre I, Daujat M, Aubert BS, Bories P, et al. Omeprazole is an aryl hydrocarbon-like inducer of human hepatic cytochrome P450. Gastroenterology 99: 737-747, 1990

Dickins M, Bridges JW. The relationship between the binding of 2-n-alkylbenzimidazoles to rat hepatic microsomal cytochrome P-450 and the inhibition of monooxygenation. Biochemical Pharmacology 31: 1315-1320, 1982

Eichelbaum M, Gross AS. The genetic polymorphism of debrisoquine/sparteine metabolism - clinical aspects. Pharmacology and Therapeutics 46: 377-394, 1990

Ekenved G, Elofsson R, Sölvell L. Bioavailability studies on a buffered acetylsalicylic acid preparation. Acta Pharmacologica Suecica 12: 323-332, 1975

Fellenius E, Berglindh T, Sachs G, Olbe L, Elander B, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H^++K^+)ATPase. Nature 290: 159-161, 1981

Funck-Brentano C, Turgeon J, Woosley RL, Roden DM. Effect of low dose quinidine on encainide pharmacokinetics and pharmacodynamics. Influence of genetic polymorphism. Journal of Pharmacology and Experimental Therapeutics 249: 134-142, 1989

Gault H, Kalra J, Ahmed M, Kephay D, Barrowman J. Influence of gastric pH on digoxin biotransformation I: intragastric hydrolysis. Clinical Pharmacology and Therapeutics 27: 16-21, 1980

Ged C, Rouillon JM, Pichard L, Combalbert J, Bressot N, et al. The increase in urinary excretion of 6β-hydroxycortisol as a marker of human hepatic cytochrome P450IIIA induction. British Journal of Clinical Pharmacology 28: 373-387, 1989

Genève J, Taburet AM, Bocquentin M, Simoneau G, Caulin C, et al. Effect of omeprazole on theophylline metabolism in healthy subjects. Abstract. Gastroenterology 100: A69, 1991

Gonzalez FJ. The molecular biology of cytochrome P450s. Pharmacological Reviews 40: 243-288, 1989

Gonzalez FJ, Schmid BJ, Umeno M, McBride OW, Hardwick JP, et al. Human P450PCN1: sequence, chromosome localization, and direct evidence through cDNA expression that P450PCN1 is nifedipine oxidase. DNA 7: 79-86, 1988

Grant DM, Campbell ME, Tang BK, Kalow W. Biotransformation of caffeine by microsomes from human liver. Biochemical Pharmacology 36: 1251-1260, 1987

Guengerich FP. Oxidation of 17α-ethynylestradiol by human liver cytochrome P-450. Molecular Pharmacology 33: 500-508, 1988

Guengerich FP. Polymorphisms of cytochrome P-450 in humans. Trends in Pharmacological Science 10: 107-109, 1989

Guengerich FP, Müller-Enoch D, Blair IA. Oxidation of quinidine by human liver cytochrome P-450. Molecular Pharmacology 30: 287-295, 1986

Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism - studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. Gastroenterology 89: 1235-1241, 1985

Gugler R, Jensen JC. Drugs other than H_2-receptor antagonists as clinically important inhibitors of drug metabolism in vivo. Pharmacology and Therapeutics 33: 133-137, 1987

Haefeli W, Bargetzi MJ, Follath F, Meyer UA. Potent inhibition of cytochrome P450IID6 (debrisoquine 4-hydroxylase) by flecainide in vitro and in vivo. Journal of Cardiovascular Pharmacology 15: 776-779, 1990

Henry DA, Somerville KW, Kitchingman G, Langman MJS. Omeprazole: effects on oxidative drug metabolism. British Journal of Clinical Pharmacology 18: 195-200, 1984

Henry D, Brent P, Whyte I, Mihaly G, Devenish-Meares S. Propranolol steady-state pharmacokinetics are unaltered by omeprazole. European Journal of Clinical Pharmacology 33: 369-373, 1987

Hetzel DJ, Dent J, Reed WD, Narielvala FM, Mackinnon M, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 95: 903-912, 1988

Jönsson KÅ, Jones AW, Boström H, Andersson T. No influence of omeprazole on the pharmacokinetics of ethanol in healthy men. Abstract no. PD201. Abstracts II, World Congresses of Gastroenterology, Sydney, Australia, 26-31 August, 1990

Klinkenberg-Knol EC, Jansen JMBJ. Festen HPM, Meuwissen SGM, Lamers CBHW. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. Lancet 1: 349-351, 1987

Knodell RG, Dubey RK, Wilkinson GR, Guengerich FP. Oxidative metabolism of hexobarbital in human liver: relationship to polymorphic S-mephenytoin 4-hydroxylation. Journal of Pharmacology and Experimental Therapeutics 245: 845-849, 1988

Kronbach T, Fischer V, Meyer UA. Cyclosporine metabolism in human liver: identification of a cytochrome P-450III gene family as the major cyclosporine-metabolizing enzyme explains interactions of cyclosporine with other drugs. Clinical Pharmacology and Therapeutics 43: 630-635, 1988

Kronbach T, Mathys D, Umeno M, Gonzalez FJ, Meyer UA. Oxidation of midazolam and triazolam by human liver cytochrome P450IIIA4. Molecular Pharmacology 36: 89-96, 1989

Küpfer A, Branch RA. Stereoselective mephobarbital hydroxylation co-segregates with mephenytoin hydroxylation. Clinical Pharmacology and Therapeutics 38: 414-418, 1985

Küpfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. European Journal of Clinical Pharmacology 26: 753-759, 1984

Lennard MS. The polymorphic oxidation of beta-adrenoceptor antagonists. Pharmacology and Therapeutics 41: 461-477, 1989

Lind T, Andersson T, Skånberg I, Olbe L. Biliary excretion of intravenous [^{14}C]omeprazole in humans. Clinical Pharmacology and Therapeutics 42: 504-508, 1987

Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole - a gastric proton pump inhibitor - on pentagastrin stimulated acid secretion in man. Gut 24: 270-276, 1983

Lindberg P, Nordberg P, Alminger T, Brändström A, Wallmark B. The mechanism of action of the gastric acid secretion inhibitor omeprazole. Journal of Medicinal Chemistry 29: 1327-1329, 1986

Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. Lancet 2: 584-586, 1977

Mayersohn M. Physiological factors that modify systemic drug availability and pharmacologic response in clinical practice. In Blanchard et al. (Eds) Principles and perspectives in drug bioavailability, pp. 211-273, Karger, Basel, 1979

Meier UT, Meyer UA. Genetic polymorphism of human cytochrome P-450/(S)-mephenytoin 4-hydroxylase. Studies with human autoantibodies suggest a functionally altered cytochrome P-450 isozyme as cause of the genetic deficiency. Biochemistry 26: 8466-8474, 1987

Mertz Nielsen A, Trap-Jensen J, Bonnevie O, Lech Y. Immediate effect of omeprazole and cimetidine on apparent liver blood flow in man. Scandinavian Journal of Gastroenterology 21 (Suppl. 118): 166-168, 1986

Mezey E. Ethanol metabolism and ethanol drug interactions. Biochemical Pharmacology 25: 869-875, 1976

Mitchard M, Harris A, Mullinger BM. Ranitidine drug interactions - a literature review. Pharmacology and Therapeutics 32: 293-325, 1987

Muller-Lissner S, Sonnenberg A, Blum A. Does aminopyrine clearance reflect gastric mucosal blood flow or parietal cell function? Gut 23: 997-1002, 1981

Naesdal J, Andersson T, Bodemar G, Larsson R, Regårdh CG, et al. Pharmacokinetics of [^{14}C]omeprazole in patients with impaired renal function. Clinical Pharmacology and Therapeutics 40: 344-351, 1986

Naesdal J, Bodemar G, Walan A. Effect of omeprazole, a substituted benzimidazole, on 24h intragastric acidity in patients with peptic ulcer disease. Scandinavian Journal of Gastroenterology 19: 916-922, 1984

Nebert DW, Nelson DR, Adesnik M, Coon MJ, Estabrook RW, et al. The P450 superfamily: updated listing of all genes and

recommended nomenclature for the chromosomal loci. DNA 8: 1-13, 1989
Nelson DR, Strobel HW. Evolution of cytochrome P-450 proteins. Molecular Biology and Evolution 4: 572-593, 1987
Oosterhuis B, Jonkman JHG. Omeprazole: pharmacology, pharmacokinetics and interactions. Digestion 44 (Suppl. 1): 9-17, 1989
Paulsen O, Höglund P, Walder M. No effect of omeprazole induced hypoacidity on the bioavailability of amoxycillin or bacampicillin. Scandinavian Journal of Infectious Diseases 21: 219-223, 1989
Pawlik W, Tague LL, Teppermann BL, Miller TA, Jacobson ED. Histamine H_1- and H_2-receptor vasodilation of canine intestinal circulation. American Journal of Physiology 233: E219-E224, 1977
Pichard L, Gillet G, Fabre I, Dalet-Beluche I, Bonfils C, et al. Identification of the rabbit and human cytochromes P-450IIIA as the major enzymes involved in the N-demethylation of diltiazem. Drug Metabolism and Disposition 18: 711-719, 1990
Prichard PJ, Walt RP, Kitchingman GK, Somerville KW, Langman MJS, et al. Oral phenytoin pharmacokinetics during omeprazole therapy. British Journal of Clinical Pharmacology 24: 543-545, 1987
Raucy JL, Lasker JM, Lieber CS, Black M. Acetaminophen activation by human liver cytochromes P450IIE1 and P450IA2. Archives of Biochemistry and Biophysics 271: 270-283, 1989
Regårdh CG, Andersson T, Lagerström PO, Lundborg P, Skånberg I. The pharmacokinetics of omeprazole in humans - a study of single intravenous and oral doses. Therapeutic Drug Monitoring 12: 163-172, 1990
Relling MV, Aoyama T, Gonzalez FJ, Meyer UA. Tolbutamide and mephenytoin hydroxylation by human cytochrome P450s in the CYP2C subfamily. Journal of Pharmacology and Experimental Therapeutics 252: 442-447, 1990
Robson RA, Miners JO, Matthews AP, Stupans I, Meller D, et al. Characterisation of theophylline metabolism by human liver microsomes. Biochemical Pharmacology 37: 1651-1659, 1988
Sax MJ, Sawyer WT, Cupit GC, Greenblatt DJ, Kowalsky SF, et al. Advances in Therapy 5: 153-272, 1988
Schnaper HW, Aune TM, Roby RK. A role for histamine type II (H-2) receptor binding in production of the lymphokine, soluble immune response suppressor (SIRS). Journal of Immunology 139: 1185-1190, 1987
Sesardic D, Boobis AR, Edwards RJ, Davies DS. A form of cytochrome P450 in man, orthologous to form d in the rat, catalyses the O-deethylation of phenacetin and is inducible by cigarette smoking. British Journal of Clinical Pharmacology 26: 363-372, 1988
Sesardic D, Boobis AR, Murray BP, Murray S, Segura J, et al. Furafylline is a potent and selective inhibitor of cytochrome P450IA2 in man. British Journal of Clinical Pharmacology 29: 651-663, 1990
Sharma BK, Walt RP, Pounder RE, Gomes MdeFA, Wood EC, Logan LH. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. Gut 25: 957-964, 1984
Sjövall J. Human pharmacokinetics of aminopenicillins, Thesis, Karolinska Institutet, Stockholm, 1985
Skaunic V, Hulek P, Martinkova J. Changes in kinetics of exogenous dyes in the ageing process. In Kitani (Ed.) Liver and ageing, pp. 115-130, Elsevier North-Holland, Amsterdam, 1978
Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. Clinical Pharmacokinetics 15: 44-56, 1988
Steiner E, Spina E. Differences in the inhibitory effect of cimetidine on desipramine metabolism between rapid and slow debrisoquin hydroxylators. Clinical Pharmacology and Therapeutics 42: 278-282, 1987
Sutfin T, Balmér K, Boström H, Eriksson S, Höglund P, Paulsen O. Stereoselective interaction of omeprazole with warfarin in healthy men. Therapeutic Drug Monitoring 11: 176-184, 1989
Sölvell L. Clinical safety of omeprazole. Canadian Journal of Gastroenterology 3 (Suppl. A): 91A-97A, 1989
Veronese ME, Doecke CJ, McManus ME, Sansom LN, Miners JO, et al. Relationship between the human microsomal metabolism of tolbutamide and phenytoin. Abstract no. A383. In Ingelman-Sundberg, et al. (Eds) Drug metabolising enzymes: genetics, regulation and toxicology. Proceedings of the VIIth International Symposium on Microsomes and Drug Oxidations, Stockholm, Karolinska Institutet, June 25-29, 1990
Vessel ES. The antipyrine test in clinical pharmacology: conceptions and misconceptions. Clinical Pharmacology and Therapeutics 26: 272-286, 1979
Wagner F, Kalusche D, Trenk D, Jähnchen E, Roskamm H. Drug interaction between propafenone and metoprolol. British Journal of Clinical Pharmacology 24: 213-220, 1987
Walan A, Bader JP, Classen M, Lamers CBHW, Piper DW, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. New England Journal of Medicine 320: 69-75, 1989
Ward SA, Walle T, Walle UK, Wilkinson GR, Branch RA. Propranolol's metabolism is determined by both mephenytoin and debrisoquin hydroxylase activities. Clinical Pharmacology and Therapeutics 45: 72-79, 1989
Watkins PB, Murray SA, Thomas PE, Wrighton SA. Distribution of cytochromes P-450, cytochrome b_5, and NADPH-cytochrome P-450 reductase in an entire human liver. Biochemical Pharmacology 39: 471-476, 1990
Watkins PB, Wrighton SA, Maurel P, Schuetz EG, Mendez-Picon G, et al. Identification of an inducible form of cytochrome P-450 in human liver. Proceedings of the National Academy of Sciences of the United States of America 82: 6310-6314, 1985
Wilkinson GR, Guengerich FP, Branch RA. Genetic polymorphism of S-mephenytoin hydroxylation. Pharmacology and Therapeutics 43: 53-76, 1989
Wrighton SA, Brian WR, Sari MA, Iwasaki M, Guengerich FP, et al. Studies on the expression and metabolic capabilities of human liver cytochrome P450IIIA5 (HLp3). Molecular Pharmacology 38: 207-213, 1990
Wrighton SA, Thomas PE, Molowa DT, Haniu M, Shively JE, et al. Characterization of ethanol-inducible human liver N-nitrosodimethylamine demethylase. Biochemistry (USA) 25: 6731-6735, 1986
Wynne HA, Goudevenos J, Rawlins MD, James OFW, Adams PC, et al. Hepatic drug clearance: the effect of age using indocyanine green as a model compound. British Journal of Clinical Pharmacology 30: 634-637, 1990
Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (Part I). Clinical Pharmacokinetics 19: 319-332, 1990a
Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (Part II). Clinical Pharmacokinetics 19: 400-415, 1990b

Correspondence and reprints: *Tommy Andersson*, Department of Clinical Pharmacology, Research Laboratories, AB Hässle, S-431 83 Mölndal, Sweden.