Drug Safety 1997 Mar, 16 (3): 171-179
0114-5916/97/0003-0171/$04.50/0

Drug Interactions with Proton Pump Inhibitors

Peter Unge[1] and *Tommy Andersson*[2]

1 Department of Medicine, Sandviken Hospital, Sandviken, Sweden
2 Astra Hässle AB, Mölndal, Sweden

Contents

Summary

Omeprazole, lansoprazole and pantoprazole are all mainly metabolised by the polymorphically expressed cytochrome P450 (CYP) isoform CYP2C19 (*S*-mephenytoin hydroxylase). All 3 proton pump inhibitors have a very limited potential for drug interactions at the CYP level. Small effects on CYP reported for these compounds are usually of no clinical relevance. No dose related adverse effects have been identified, suggesting that the small proportion of slow metabolisers is at no additional risk for clinically important drug interactions.

The absorption of some compounds, e.g. benzylpenicillin (penicillin G), are altered during treatment with proton pump inhibitors as a result of the increased intragastric pH. A synergy has been confirmed between omeprazole and amoxicillin or clarithromycin in the antibacterial effect against *Helicobacter pylori*.

Proton pump inhibitors are substituted benzimidazoles which suppress gastric acid secretion by inhibition of the H^+,K^+-ATPase in the parietal cell.[1-3] The degree of acid inhibition correlates well with the area under the plasma concentration versus time curve (AUC) for omeprazole and is not directly related to the plasma concentration of the drug.[4] A similar correlation is expected for lansoprazole and pantoprazole. The long duration of acid inhibition (48 to 72 hours) depends on the prolonged irreversible binding of the active form of the drug (sulphenamide), which is formed and trapped in the acidic compartment of the parietal cell, to the enzyme H^+,K^+-ATPase in the parietal cells.[5]

With the increasing use of proton pump inhibitors in the community it is important to be aware of any potentially clinically relevant drug-drug

interactions. The interactions of omeprazole, lansoprazole and pantoprazole have been extensively reviewed by Andersson[6] and the present review aims to put emphasis on the potential clinical significance of metabolic drug interactions with these drugs.

1. Interactions with Proton Pump Inhibitors at the Absorption Level

Proton pump inhibitors are rapidly degraded in an acidic milieu and are therefore administered in formulations that aim to avoid contact with acid. Food does not seem to influence the amount of omeprazole that is absorbed,[7,8] while lansoprazole absorption is both delayed and decreased by food and pantoprazole absorption is delayed by food intake.[9-11] A plausible explanation might be differences in the acid protective layer of the oral formulation of these drugs, and is not dependent on the drug *per se*. The significance of these findings would probably be less at steady state, i.e. at repeated administration. In addition, there is no effect of antacids on the absorption of omeprazole and pantoprazole, but a slight reduction in bioavailability has been reported for lansoprazole.[10,12,13]

Following therapeutic doses of proton pump inhibitors, intragastric pH will be elevated from untreated values of pH 1 to 2 to values to around pH 3 to 5 or above.[14] To overcome the hydrolysis within the normally acidic stomach, a number of antibacterials, such as penicillins and tetracyclines, are formulated as enteric coated tablets or esters.[15] The rate and/or extent of absorption of such drugs might be altered according to the degree of inhibition of gastric acid secretion, and, thus elevation of pH.

During treatment with omeprazole 20 mg/day the absorption of digoxin and nifedipine was increased by 10% and 26%, respectively, increases considered as unlikely to be of any clinical significance.[16,17] The urinary excretion of unchanged digoxin was also shown to increase during omeprazole treatment,[18] which may indicate a corresponding increase in absorption. The absorption of amoxicillin and bacampicillin was not influenced by omeprazole treatment,[19] while the absorption of benzylpenicillin was increased by 10-fold.[20] Any influence of lansoprazole treatment on the absorption of other drugs has not been published. Treatment with pantoprazole 40 mg/day resulted in an increased absorption of digoxin by 10%,[21] i.e. similar to that reported for omeprazole. A slight increase in the absorption of nifedipine by 7% did not reach statistical significance.[22] The influence on ketoconazole absorption has not been not studied with any of the proton pump inhibitors, but a decreased absorption of this drug is expected.[23]

In summary, an effect of proton pump inhibitors on the absorption of other drugs that, for various reasons, have a pH dependent absorption process is expected.

2. Interactions with Proton Pump Inhibitors at the Metabolism Level

2.1 Metabolism in General

Metabolism is the overall name for oxidation, hydroxylation, and hydrolysis, mainly associated with the cytochrome P450 (CYP) system of enzymes. It also covers phase II reactions, i.e. conjugation reactions, where the molecule is conjugated to endogenous inactive compounds. CYP includes 13 different families and 22 subfamilies.[24] Each subfamily contains one or more specific CYP isoforms (>60 in total). The similarity in amino acid sequence of the proteins determines to which family or subfamily they belong. Six different CYP isoforms are of particular importance in drug metabolism in general; CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. Based on which CYP isoform is mainly responsible for the metabolism of the drugs, the relative contribution of this CYP isoform to the total metabolism of the drugs, the relative affinities of the drugs for this CYP isoform, and the relative concentrations of the drugs in the hepatocytes as judged from plasma concentrations, it is possible to predict whether the compounds are likely or not likely to interact with each other on the CYP level.[6] If 2 drugs are metabolised by the same CYP isoform, a competitive inhibition can be predicted,

and the metabolism of the drug with least affinity to the enzyme will probably be inhibited to varying extent. Most CYP isoforms can be induced, resulting in an increased metabolic rate for substrates of this enzyme.

A couple of the CYP isoforms (CYP2C19 and CYP2D6) are polymorphically expressed, which means that a few individuals, i.e. the poor metabolisers, among the population lack activity of the enzyme.[25] Metabolism may still occur in such poor metabolisers, although at a slower rate and by other CYP isoforms. Metabolism of a compound via one CYP isoform does not exclude potential for inhibition or induction of other CYP isoforms not being involved in its own metabolism.[26]

2.2 Metabolism of Proton Pump Inhibitors

The primary and secondary metabolism of omeprazole has been thoroughly investigated, and the major enzyme involved in omeprazole metabolism is CYP2C19 (fig. 1).[27-34] However, a few individuals lack activity of CYP2C19 (Caucasians ≈3%, Japanese, Chinese, and Koreans ≈15%) and metabolise omeprazole more slowly compared to the majority of people.[27,29-31] These individuals have omeprazole AUCs that are approximately 5 times higher than those seen in an average individual[6] and plasma elimination half-lives that are approximately 3 times longer (2.1 versus 0.7 hours). CYP3A is to a lesser extent involved in the metabolism of omeprazole, but, since its affinity for CYP2C19 is several fold higher than for CYP3A, omeprazole has a potential to inhibit the metabolism of substrates for CYP2C19 but not substrates for CYP3A. No involvement of the other major CYP isoforms has been demonstrated for omeprazole.

Both lansoprazole[35] and pantoprazole[9,36,37] seem to be dependent on these same CYP isoforms for their major metabolism (fig.1). The difference in AUC between CYP2C19 deficient people and average individuals for lansoprazole and pantoprazole is similar to that reported for omeprazole, indicating that an equal proportion of the total metabolism of all 3 compounds is dependent on CYP2C19.[6] The elimination half-lives in

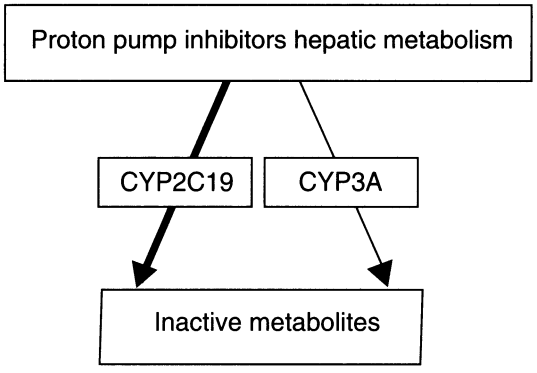

Fig. 1. Metabolism of proton pump inhibitors. *Abbreviation:* CYP = cytochrome P450.

CYP2C19 deficient individuals were approximately 4 and 6 hours for lansoprazole and pantoprazole, respectively. Corresponding values in normal, rapid metabolisers are approximately 1.5 and 1.3 hours, respectively.[9,35,37] However, since the elimination half-lives in poor metabolisers in relation to the dosing interval (24 hours) of these compounds still is short, this will probably be of minor clinical relevance.

A summary of the results of interaction studies for omeprazole, lansoprazole and pantoprazole with specific CYP substrates is given in tables I, II and III.

2.3 Cytochrome P450 (CYP)

2.3.1 CYP1A2

CYP1A2 is induced in cigarette smokers and by ingestion of charcoal broiled beef as well as by high intake of cruciferous vegetables.[38-40] Substrates for this enzyme are, for instance, caffeine, phenacetin and theophylline.[41-45]

Omeprazole 20 to 40mg given to 'normal' rapid metabolisers does not influence the metabolism of CYP1A2 substrates, but, in slow metabolisers, omeprazole 40mg seems to increase the metabolism of caffeine by 30%.[46-51] Lansoprazole decreased the theophylline AUC by 13%, indicative of a small induction of CYP1A2.[52] Intravenous administration of pantoprazole 30mg had no effect on the plasma concentration of theophylline.[37]

Table I. Interaction studies with omeprazole and cytochrome P450 (CYP) specific substrates

CYP1A2[46-51]	CYP2C9[59-62,65,66]	CYP2C19[59-62,65,66]	CYP2D6[81,82]	CYP2E1[87-90]	CYP3A4[17,99-103]
Caffeine	Phenytoin	Diazepam	Metoprolol	Ethanol	Cyclosporin
Phenacetin	*S*-Warfarin	Phenytoin[a]	Propranolol[a]		Erythromycin
Theophylline		*R*-Warfarin[a]			Estradiol
					Lidocaine (lignocaine)
					Nifedipine
					Quinidine

a Partly substrate.

However, since intravenous administration leads to lower exposure of the liver to pantoprazole than oral administration it can be questioned whether oral administration of therapeutic doses (40mg) of pantoprazole would present the same results.

2.3.2 CYP2C9

CYP2C9 is mainly responsible for the metabolism of phenytoin, tolbutamide, and *S*-warfarin, the most potent of the 2 warfarin enantiomers.[53-58]

Omeprazole 40 mg/day given for 1 week increased plasma phenytoin concentrations by 15 to 20% in 2 independent studies,[59,60] while a third study showed no effect.[61] This is probably a result of an inhibition of a minor pathway of phenytoin metabolism mediated via CYP2C19.[54] Omeprazole 20 mg/day administered for 3 weeks had no effect on the plasma concentration of phenytoin in patients with epilepsy receiving continuous treatment with this agent.[62] Pantoprazole 40 mg/day and lansoprazole 60 mg/day did not show any significant interaction with phenytoin.[63,64]

Omeprazole, lansoprazole and pantoprazole had either no effect or only minor effects on the plasma concentrations of *S*-warfarin.[65-68] In 1 of these studies omeprazole was given to anticoagulated patients receiving continuous treatment with warfarin.[66]

Omeprazole 40 mg/day has been shown to increase the AUC of tolbutamide by 10%,[69] but, as for phenytoin, this probably reflects inhibition of a minor metabolic pathway for tolbutamide via CYP2C19.[56,70] This interaction is of no clinical relevance. Data on lansoprazole and pantoprazole with respect to tolbutamide are lacking.

The effects of omeprazole, lansoprazole, and pantoprazole on the metabolism of CYP2C9 substrates seem to be without clinical significance, both in terms of plasma concentrations and clinical effect on patients.

2.3.3 CYP2C19 (S-Mephenytoin hydroxylase)

CYP2C19 (*S*-mephenytoin hydroxylase) is polymorphically expressed and mediates the major metabolic transformations of all 3 proton pump inhibitors referred to in this review. Examples of substrates for CYP2C19 are diazepam and cycloguanil, as well as partly phenytoin, *R*-warfarin, and tolbutamide as indicated in section 2.3.2.[54,56,58,70-74]

Omeprazole partly inhibits the metabolism of diazepam.[59,75,76] The clearance of diazepam was decreased by approximately 25% during treatment with omeprazole 20 mg/day. No effect was seen in slow metabolisers, since these individuals lack CYP2C19.[75] Oral lansoprazole 60 mg/day, and intravenous pantoprazole 240 mg/day, did not inhibit

Table II. Interaction studies with lansoprazole and cytochrome P450 (CYP) specific substrates

CYP1A2[52]	CYP2C9[63,67]	CYP2C19[63,67]	CYP2D6[84]	CYP2E1[91]	CYP3A4
Theophylline	Phenytoin	Diazepam	Propranolol[a]	Ethanol	
	S-Warfarin?	Phenytoin[a]			
		R-Warfarin[a]			

a Partly substrate.

Table III. Interaction studies with pantoprazole and cytochrome P450 (CYP) specific substrates

CYP1A2[37]	CYP2CP[64,68]	CYP2C19[64,68]	CYP2D6[85]	CYP2E1[92]	CYP3A4[22]
Theophylline[a]	Phenytoin	Diazepam[a]	Metoprolol	Ethanol	Nifedipine
	S-Warfarin	Phenytoin[b]			
		R-Warfarin[b]			

a Pantoprazole administered intravenously.
b Partly substrate.

the metabolism of diazepam.[77,78] A 10% increase in the plasma concentrations of *R*-warfarin was demonstrated in 2 studies with omeprazole, one of which was performed in anti-coagulated patients.[65,66] Omeprazole had no effect on coagulation time in these patients.[66] Pantoprazole and lansoprazole have not been seen to significantly increase the plasma concentration of *R*-warfarin.[67,68] The documentation for lansoprazole, though, is scarce.

Omeprazole inhibits the metabolism of substrates for CYP2C19, as indicated by its influence on diazepam, an interaction which probably has no clinical significance. Lansoprazole appears to be a less potent CYP2C19 inhibitor. It is not possible to make an adequate comparison for pantoprazole, since it was administered intravenously.

2.3.4 CYP2CD6 (Debrisoquine hydroxylase)

CYP2D6 (debrisoquine hydroxylase) is polymorphically expressed and the frequency of slow/poor metabolisers is approximately 7% among Caucasians, and as low as 1% in Asians.[79] Various β-blockers, antiarrhythmics, and antidepressants are the most common substrates of CYP2D6.[6] Omeprazole does not interact with propanolol and metoprolol, lansoprazole does not interact with propranolol and pantoprazole does not interact with metoprolol.[80-85]

2.3.5 CYP2E1

CYP2E1 metabolises low weight chemicals and a common substrate is ethanol.[86] None of the proton pump inhibitors reviewed here appear to interfere with the metabolism of ethanol.[87-92]

2.3.6 CYP3A4

CYP3A4 is probably the most important CYP isoform for drug metabolism in general, because the majority of drugs tested so far are metabolised via this isoform. Induction can be seen with some commonly used drugs.[24] Substrates of CYP3A4 are cyclosporin, erythromycin, estradiol, lidocaine (lignocaine), nifedipine, quinidine.[93-98]

Omeprazole 20 to 40 mg/day did not influence the metabolism of cyclosporin,[99] erythromycin,[100] estradiol,[101] lidocaine,[102] nifedipine,[17] or quinidine.[103] None of the proton pump inhibitors reviewed interact with oral contraceptive pills containing levonorgestrel and ethinylestradiol, which are both potential substrates for CYP3A4.[104-107] The biotransformation of prednisone to prednisolone and subsequent disposition of prednisolone are not affected by omeprazole or lansoprazole.[108] A recent study in healthy volunteers suggests that omeprazole treatment increases the AUC of carbamazepine,[109] a potential substrate for CYP3A4,[110] but these results contradict a retrospective study in patients receiving continuous carbamazepine treatment.[111] Omeprazole 120 mg/day, and pantoprazole 40 mg/day, did not change the urinary excretion of 6β-hydroxycortisol,[112,113] indicating that these drugs do not induce CYP3A4.

Omeprazole does not interact with the metabolism of CYP3A4 substrates. Data on lansoprazole and pantoprazole are limited but do not suggest any clinically important interactions via CYP3A4.

2.4 *N*-Acetyl Transferase

N-Acetyl transferase is polymorphically expressed and approximately half of the Caucasian population exhibits slow metabolism of *N*-acetyl transferase substrates, such as isoniazid, procainamide, hydralazine, sulfasalazine, sulfadimidine, dapsone, nitrazepam, and clonazepam.[114] Om-

eprazole does not influence the metabolic activity of *N*-acetyl transferase.[46] Data on lansoprazole and pantoprazole are lacking.

2.5 Unknown Mechanisms

A placebo controlled study of omeprazole 40 mg/day given together with clarithromycin showed a significantly increased AUC for omeprazole but did not alter the intragastric pH.[115] Also the AUC of clarithromycin was increased significantly. Whether these effects are due to altered absorption or inhibition of metabolism or both is not clear. However, this phenomenon might partly explain the synergism in the anti-bacterial efficacy against *Helicobacter pylori* of concomitant therapy with omeprazole and clarithromycin. Similar interactions might be true also between clarithromycin and lansoprazole or pantoprazole, but corresponding data are lacking.

3. Clinical Relevance

The 3 proton pump inhibitors reviewed seem to have a very limited potential for drug interactions at the CYP level and thus for influencing the metabolism of other drugs, but data on lansoprazole and pantoprazole are limited in this respect.

Slow metabolisers of all 3 proton pump inhibitors exhibit higher than average plasma concentrations of these drugs, as a consequence of the genetic constitution of these individuals; they lack activity of the enzyme (CYP2C19) which is responsible for the major metabolism of omeprazole, lansoprazole, and pantoprazole. Since all 3 compounds are considered well tolerated, and no dose related adverse effects have been identified, this finding is of no clinical relevance.

The absorption of some compounds, e.g. digoxin, might be altered as a result of the increased gastric pH obtained during treatment with proton pump inhibitors. Similar effects are expected irrespective of which proton pump inhibitor is given. Potentially, this type of interaction could have some clinical relevance, but no data are so far available to indicate this. This alteration of absorption might be exploited as an option to allow oral administration of acid labile drugs during pronounced acid inhibition replacing the need for intravenous administration.

4. Conclusion

In conclusion, omeprazole, lansoprazole, and pantoprazole are structurally very similar, and an evaluation of available data indicate that they demonstrate generally very similar properties with respect to metabolism and interactions. No clinically important interactions have so far been confirmed with these compounds.

References

1. Fellenius E, Berglindh T, Sachs G, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H^++ K^+)ATPase. Nature 1981; 290: 159-61
2. Lindberg P, Nordberg P, Alminger T, et al. The mechanism of action of the gastric acid secretion inhibitor omeprazole. J Med Chem 1986; 29: 1327-9
3. Shin JM, Besancon M, Prinz C, et al. Continuing development of acid pump inhibitors: site of action of pantoprazole. Aliment Pharmacol Ther 1994; 8 Suppl. 1: 11-23
4. Lind T, Cederberg C, Ekenved G, et al. Effect of omeprazole – a gastric proton pump inhibitor – on pentagastrin stimulated acid secretion in man. Gut 1983; 24: 270-6
5. Brändström A, Lindberg P, Bergman NÅ, et al. Chemical reactions of omeprazole and omeprazole analogues. Acta Chem Scand 1989; 43: 536-611
6. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Clin Pharmacokinet 1996; 31 (1): 9-28
7. Pilbrant Å, Cederberg C. Development of an oral formulation of omeprazole. Scand J Gastroenterol 1985; 20 Suppl. 108: 113-20
8. Andersson T, Andrén K, Cederberg C, et al. Bioavailability of omeprazole as enteric coated (EC) granules in conjunction with food on the first and seventh days of treatment. Drug Invest 1990; 2: 184-8
9. Benet LZ, Zech K. Pharmacokinetics – a relevant factor for the choice of a drug? Aliment Pharmacol Ther 1994; 8 Suppl. 1: 25-32
10. Delhotal-Landes B, Cournot A, Vermerie N, et al. The effect of food and antacids on lansoprazole absorption and disposition. Eur J Drug Metab Dispos 1991; Special Issue No III: 315-20
11. Bergstrand R, Grind M, Nyberg G, et al. Decreased oral bioavailability of lansoprazole in healthy volunteers when given with a standardised breakfast. Clin Drug Invest 1995; 9: 67-71
12. Tuynman HARE, Festen HPM, Röhss K. Lack of effect of antacids on plasma concentrations of omeprazole given as enteric-coated granules. Br J Clin Pharmacol 1987; 24; 833-5
13. Hartmann M, Bliesath H, Huber R, et al. Lack of influence of antacids on the pharmacokinetics of the new gastric H^+/ K^+-ATPase inhibitor pantoprazole [abstract]. Gastroenterology 1994; 106 Suppl.: A91
14. Lanzon-Miller S, Pounder RE, Hamilton MR, et al. Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment Pharmacol Ther 1987; 1: 239-51

15. Mayersohn M. Physiological factors that modify systemic drug availability and pharmacologic response in clinical practice. In: Blanchard et al., editors. Principles and perspectives in drug bioavailability. Basel: Karger, 1979: 211-73
16. Oosterhuis B, Jonkman JHG, Andersson T, et al. Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. Br J Clin Pharmacol 1991; 32: 569-72
17. Soons PA, van den Berg G, Danhof M, et al. Influence of single- and multiple-dose omeprazole treatment on nifedipine pharmacokinetics and effects in healthy subjects. Eur J Clin Pharmacol 1992; 42: 319-24
18. Cohen AF, Kroon R, Schoemaker R, et al. Influence of gastric acidity on the bioavailability of digoxin. Ann Intern Med 1991; 115: 540-5
19. Paulsen O, Höglund P, Walder M. No effect of omeprazole induced hypoacidity on the bioavailability of amoxycillin or bacampicillin. Scand J Infect Dis 1989; 21: 219-23
20. Bergstrand R, Idström JP, Eriksson S. Bioavailability of penicillin during omeprazole treatment. Sweden: Astra Hässle AB, 1996 (Data on file)
21. Hartmann M, Huber R, Bliesath H, et al. Lack of interaction between pantoprazole and digoxin at therapeutic doses in man [Abstracts]. In: Management of acid-related diseases: focus on pantoprazole. Berlin: Charité, 1993: 34-5
22. Bliesath H, Huber R, Hartmann M, et al. Pantoprazole does not influence the steady-state pharmacokinetics of nifedipine [abstract]. Gastroenterol 1994; 106 Suppl.: A55
23. Piscitelli SC, Goss TF, Wilton JH, et al. Effects of ranitidine and sucralfate on ketoconazole bioavailability. Antimicrob Agents Chemother 1991; 35: 1765-71
24. Nebert DW, McKinnon RA. Cytochrome P450: evolution and functional diversity. In: Prog Liver Dis 1994; 12: 63-97
25. de Morais SMF, Wilkinson GR, Blaisdell J, et al. The major genetic defect responsible for the polymorphism of *S*-mephenytoin metabolism in humans. J Biol Chem 1994; 269: 15419-22
26. Nielsen MD, Brösen K, Gram LF. A dose – effect study of the *in vivo* inhibitory effect of quinidine on sparteine oxidation in man. Br J Clin Pharmacol 1990; 29: 299-304
27. Goldstein JA, Faletto MB, Romkes-Sparks M, et al. Evidence that CYP2C19 is the major (S)-mephenytoin 4′-hydroxylase in humans. Biochemistry 1994; 33: 1743-52
28. Andersson T, Regårdh CG, Dahl-Puustinen ML, et al. Slow omeprazole metabolizers are also poor *S*-mephenytoin hydroxylators. Ther Drug Monit 1990; 12: 415-6
29. Andersson T, Regårdh CG, Lou YC, et al. Polymorphic hydroxylation of *S*-mephenytoin and omeprazole metabolism in Caucasian and Chinese subjects. Pharmacogenetics 1992; 2: 25-31
30. Sohn DR, Kobayashi K, Chiba K, et al. Disposition kinetics and metabolism of omeprazole in extensive and poor metabolizers of *S*-mephenytoin 4-hydroxylation recruited from an oriental population. J Pharmacol Exp Ther 1992; 262: 1195-202
31. Ishizaki T, Sohn DR, Kobayashi K, et al. Interethnic differences in omeprazole metabolism in the two *S*-mephenytoin hydroxylation phenotypes studied in Caucasians and Orientals. Ther Drug Monit 1994; 16: 214-5
32. Andersson T, Miners JO, Veronese ME, et al. Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. Br J Clin Pharmacol 1993; 36: 521-30
33. Chiba K, Kobayashi K, Manabe K, et al. Oxidative metabolism of omeprazole in human liver microsomes: cosegregation with S-mephenytoin 4′-hydroxylation. J Pharmacol Exp Ther 1993; 266: 52-9
34. Andersson T, Miners JO, Veronese ME, et al. Identification of human liver cytochrome P450 isoforms mediating secondary omeprazole metabolism. Br J Clin Pharmacol 1994; 37: 597-604
35. Tucker GT. The interaction of proton pump inhibitors with cytochromes P450. Aliment Pharmacol Ther 1994; 8 Suppl. 1: 33-8
36. Huber R, Kohl B, Sachs G, et al. Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. Aliment Pharmacol Ther 1995; 9: 363-78
37. Schultz HU, Hartmann M, Steinijans VW, et al. Lack of influence of pantoprazole on the disposition kinetics of theophylline in man. Int J Clin Pharmacol Ther Toxicol 1991; 29: 369-75
38. Pantuck EJ, Hsiao KC, Maggio A, et al. Effect of cigarette smoking on phenacetin metabolism. Clin Pharmacol Ther 1974; 15: 9-17
39. Pantuck EJ, Pantuck CB, Garland WA, et al. Stimulatory effect of brussel sprouts and cabbage on human drug metabolism. Clin Pharmacol Ther 1979; 25: 88-95
40. Conney AH, Pantuck EJ, Hsiao KC, et al. Enhanced phenacetin metabolism in human subjects fed charcoal-broiled beef. Clin Pharmacol Ther 1976; 20: 633-42
41. Grant DM, Campbell ME, Tang BK, et al. Biotransformation of caffeine by microsomes from human liver. Biochem Pharmacol 1987; 36: 1251-60
42. Sesardic D, Boobis AR, Edwards RJ, et al. 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. Br J Clin Pharmacol 1988; 26: 363-72
43. Robson RA, Miners JO, Matthews AP, et al. Characterisation of theophylline metabolism by human liver microsomes. Biochem Pharmacol 1988; 37: 1651-9
44. Sarkar MA, Hunt C, Guzelian PS, et al. Characterisation of human liver cytochromes P450 involved in theophylline metabolism. Drug Metab Dispos 1992; 20: 31-7
45. Zhang ZY, Kaminsky LS. Characterisation of human cytochromes P450 involved in theophylline 8-hydroxylation. Biochem Pharmacol 1995; 50: 205-11
46. Andersson T, Bergstrand R, Cederberg C, et al. Omeprazole treatment does not affect the metabolism of caffeine. Gastroenterology 1991; 101: 943-7
47. Rost KL, Brösicke H, Brockmöller J, et al. Increase of cytochrome P4501A2 activity by omeprazole: evidence by the ^{13}C-(*N*-3-methyl)-caffeine breath test in poor and extensive metabolizers of *S*-mephenytoin. Clin Pharmacol Ther 1992; 52: 170-80
48. Xiaodong S, Gatti G, Bartoli A, et al. Omeprazole does not enhance the metabolism of phenacetin, a marker of CYP1A2 activity, in healthy volunteers. Ther Drug Monit 1994; 16: 248-50
49. Gugler R, Jensen JC. Drugs other than H2-receptor antagonists as clinically important inhibitors of drug metabolism *in vivo*. Pharmacol Ther 1987; 33: 133-7
50. Oosterhuis B, Jonkman JHG, Andersson T, et al. No influence of single intravenous doses of omeprazole on theophylline elimination kinetics. J Clin Pharmacol 1992; 32: 470-5
51. Taburet AM, Geneve J, Bocquentin M, et al. Theophylline steady state pharmacokinetics is not altered by omeprazole. Eur J Clin Pharmacol 1992; 42: 343-5
52. Granneman G, Winters EP, Locke CS, et al. Lack of effect of concomitant lansoprazole on steady state theophylline pharmacokinetics [abstract]. Gastroenterology 1991; 100: A75

53. Doecke CJ, Veronese ME, Pond SM, et al. Relationship between phenytoin and tolbutamide hydroxylations in human liver microsomes. Br J Clin Pharmacol 1991; 31: 125-30
54. Yasumori T, Chen LS, Li QH, et al. Regio- and stereo-selective metabolism of phenytoin by cytochrome P450s in human livers [abstract]. Proceedings from 10th International Symposium on Microsomes & Drug Oxidations: 1994 Jul 18-21; Toronto, Canada; 588
55. Relling MV, Aoyama T, Gonzales FJ, et al. Tolbutamide and mephenytoin hydroxylation by human cytochrome P450s in the CYP2C subfamily. J Pharmacol Exp Ther 1990; 252: 442-7
56. Chen LS, Yasumori T, Yamazoe Y, et al. Hepatic microsomal tolbutamide hydroxylation in Japanese: *in vitro* evidence for rapid and slow metabolisers. Pharmacogenetics 1993; 3: 77-85
57. Tassaneeyakul W, Veronese ME, Birkett DJ, et al. Co-regulation of phenytoin and tolbutamide metabolism in humans. Br J Clin Pharmacol 1992; 34: 494-8
58. Kaminsky LS, de Morais SM, Faletto MB, et al. Correlation of human cytochrome P450C substrate specificities with primary structure: warfarin as a probe. Mol Pharmacol 1993; 43: 234-9
59. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism- studies with diazepam and phenytoin *in vivo* and 7-ethoxycoumarin *in vitro*. Gastroenterology 1985; 89: 1235-41
60. Prichard PJ, Walt RP, Kitchingman GK, et al. Oral phenytoin pharmacokinetics during omeprazole therapy. Br J Clin Pharmacol 1987; 24: 543-5
61. Bachmann KA, Sullivan TJ, Jauregui L, et al. Absence of an inhibitory effect of omeprazole and nizatidine on phenytoin disposition, a marker of CYP2C activity. Br J Clin Pharmacol 1993; 36: 380-2
62. Andersson T, Lagerström PO, Unge P. A study of the interaction between omeprazole and phenytoin in epileptic patients. Ther Drug Monit 1990; 12: 329-33
63. Karol MD, Mukherji D, Cavanaugh JH. Lack of effect of concomitant multi-dose lansoprazole on single-dose phenytoin pharmacokinetics in subjects [abstract]. Gastroenterology 1994; 106 Suppl.: A103
64. Middle MV, Müller FO, Schall R, et al. No influence of pantoprazole on the pharmacokinetics of phenytoin. Int J Clin Pharmacol Ther 1995; 33: 304-7
65. Sutfin T, Balmér K, Boström H, et al. Stereoselective interaction of omeprazole with warfarin in healthy men. Ther Drug Monit 1989; 11: 176-84
66. Unge P, Svedberg LE, Nordgren A, et al. A study of the interaction of omeprazole and warfarin in anticoagulated patients. Br J Clin Pharmacol 1992; 34: 509-12
67. Cavanaugh JH, Winters EP, Cohen A, et al. Lack of effect of lansoprazole on steady state warfarin metabolism [abstract]. Gastroenterology 1991; 100 Suppl.: A40
68. Duursema L, Müller FO, Schall R, et al. Lack of effect of pantoprazole on the pharmacodynamics and pharmacokinetics of warfarin. Br J Clin Pharmacol 1995; 39: 700-3
69. Toon S, Holt BL, Mullins FGP, et al. Effects of cimetidine, ranitidine and omeprazole on tolbutamide metabolism. J Pharm Pharmacol 1995; 47: 85-8
70. Hall SD, Hamman MA, Rettie AE, et al. Relationships between the levels of cytochrome P4502C9 and its prototypic catalytic activities in human liver microsomes. Drug Metab Dispos 1994; 22: 975-8
71. Bertilsson L, Henthorn TK, Sanz E, et al. Importance of genetic factors in the regulation of diazepam metabolism: relationship to S-mephenytoin, but not debrisoquine, hydroxylation phenotype. Clin Pharmacol Ther 1989; 45: 348-55
72. Andersson T, Miners JO, Veronese ME, et al. Diazepam metabolism by human liver microsomes is mediated by both *S*-mephenytoin hydroxylase and CYP3A isoforms. Br J Clin Pharmacol 1994; 38: 131-7
73. Funck-Brentano C, Bosco O, Jacqz-Aigrain E, et al. Relation between chloroguanide bioactivation to cycloguanil and the genetically determined metabolism of mephenytoin in humans. Clin Pharmacol Ther 1992; 51: 507-12
74. Birkett DJ, Rees D, Andersson T, et al. *In vitro* proguanil activation to cycloguanil by human liver microsomes is mediated by CYP3A isoforms as well as by *S*-mephenytoin hydroxylase. Br J Clin Pharmacol 1994; 37: 413-20
75. Andersson T, Cederberg C, Edvardsson G, et al. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. Clin Pharmacol Ther 1990; 47: 79-85
76. Andersson T, Andrén K, Cederberg C, et al. Effect of omeprazole and cimetidine on plasma diazepam levels. Eur J Clin Pharmacol 1990; 39: 51-4
77. Lefebvre RA, Flouvat B, Karolac-Tamisier S, et al. Influence of lansoprazole treatment on diazepam plasma concentrations. Clin Pharmacol Ther 1992; 52: 458-63
78. Gugler R, Hartmann M, Rudi J, et al. Lack of interaction of pantoprazole and diazepam in man [abstract]. Gastroenterology 1992; 102 Suppl.: A77
79. Wang SL, Huang JD, Lai MD, et al. Molecular basis of genetic variation in debrisoquin hydroxylation in Chinese subjects: Polymorphism in RFLP and DNA sequence of CYP2D6. Clin Pharmacol Ther 1993; 53: 410-8
80. Lennard MS, Silas JH, Freestone S, et al. Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. Br J Clin Pharmacol 1982; 14: 301-3
81. Andersson T, Lundborg P, Regårdh CG. Lack of effect of omeprazole treatment on steady-state plasma levels of metoprolol. Eur J Clin Pharmacol 1991; 40: 61-5
82. Henry D, Brent P, Whyte I, et al. Propranolol steady-state pharmacokinetics are unaltered by omeprazole. Eur J Clin Pharmacol 1987; 33: 369-73
83. Ward SA, Walle UK, Wilkinson GR, et al. Propranolol's metabolism is determined by both mephenytoin and debrisoquin hydroxylase activities. Clin Pharmacol Ther 1989; 45: 72-9
84. Cavanaugh JH, Schneck DW, Mukherji D, et al. Lack of effect of concomitant lansoprazole on single-dose propranolol pharmacokinetics and pharmacodynamics [abstract]. Gastroenterology 1994; 106 Suppl.: A4
85. Koch HJ, Hartmann M, Bliesath H, et al. Pantoprazole does not influence metoprolol pharmacokinetics in man [abstract]. Gastroenterology 1996; 110 Suppl.: A158
86. Guengerich FP, Kim DH, Iwasaki M. Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 1991; 4: 168-79
87. Jönsson KÅ, Jones AW, Boström H, et al. Lack of effect of omeprazole, cimetidine, and ranitidine on the pharmacokinetics of ethanol in fasting male volunteers. Eur J Clin Pharmacol 1992; 42: 209-12
88. Roine R, Hernandez-Munoz R, Baraona E, et al. Effect of omeprazole on gastric first-pass metabolism of ethanol. Dig Dis Sci 1992; 37: 891-6
89. Pozzato G, Franzin F, Moretti M, et al. Effects of omeprazole on ethanol metabolism: an *in vitro* and *in vivo* rat and human study. Pharmacol Res 1994; 29: 47-58
90. Minocha A, Singh Rahal P, Brier ME, et al. Omeprazole therapy does not affect pharmacokinetics of orally administered eth-

anol in healthy male subjects. J Clin Gastroenterol 1995; 21: 107-9
91. Girre C, Coutelle C, David P, et al. Lack of effect of lansoprazole on the pharmacokinetics of ethanol in male volunteers [abstract]. Gastroenterology 1994; 106 Suppl.: A504
92. Teyssen S, Singer MV, Heinze H, et al. Pantoprazole does not influence the pharmacokinetics of ethanol in healthy volunteers [abstract]. Gastroenterology 1996; 110 Suppl.: A277
93. 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. Clin Pharmacol Ther 1988; 43: 630-5
94. Watkins PB, Wrighton SA, Maurel P, et al. Identification of an inducible form of cytochrome P-450 in human liver. Proc Natl Acad Sci USA 1985; 82: 6310-4
95. Kerlan V, Dreano Y, Bercovici JP, et al. Nature of cytochromes P450 involved in the 2-/4-hydroxylations of estradiol in human liver microsomes. Biochem Pharmacol 1992; 44: 1745-56
96. Bargetzi MJ, Aoyama T, Gonzales FJ, et al. Lidocaine metabolism in human liver microsomes by cytochrome P450IIIA4. Clin Pharmacol Ther 1989; 46: 521-7
97. Gonzalez FJ, Schmid BJ, Umeno M, et al. Human P450PCN1: sequence, chromosome localization, and direct evidence through cDNA expression that P450PCN1 is nifedipine oxidase. DNA 1988; 7: 79-86
98. Guengerich FP, Müller-Enoch D, Blair IA. Oxidation of quinidine by human liver cytochrome P-450. Mol Pharmacol 1986; 30: 287-95
99. Blohmé I, Idström JP, Andersson T. A study of the interaction between omeprazole and cyclosporine in renal transplant patients. Br J Clin Pharmacol 1993; 35: 156-60
100. Tateishi T, Graham SG, Krivoruk Y, et al. Omeprazole does not affect measured CYP3A4 activity using the erythromycin breath test. Br J Clin Pharmacol 1995; 40: 411-2
101. Galbraith RA, Michnovicz JJ. Omeprazole fails to alter the cytochrome P450-dependent 2-hydroxylation of estradiol in male volunteers. Pharmacology 1993; 47: 8-12
102. Noble DW, Bannister J, Lamont M, et al. The effect of oral omeprazole on the disposition of lignocaine. Anaesthesia 1994; 49: 497-500
103. Ching MS, Elliott SL, Stead CK, et al. Quinidine single dose pharmacokinetics and pharmacodynamics are unaltered by omeprazole. Aliment Pharmacol Ther 1991; 5: 523-31
104. Meyer BH, Maree JS, Müller FO, et al. Lack of interaction between an oral contraceptive and lansoprazole or omeprazole [abstract]. African Pharmaceutical Society Congress: 1993 Sep 21-24
105. Fuchs W, Sennewald R, Klotz U. Lansoprazole does not affect the bioavailability of oral contraceptives. Br J Clin Pharmacol 1994; 38: 376-80
106. Middle MV, Müller FO, Schall R, et al. Effect of pantoprazole on ovulation suppression by a low-dose hormonal contraceptive. Clin Drug Invest 1995; 9: 54-6
107. Ball SE, Forrester LM, Wolf CR, et al. Differences in the cytochrome P-450 isoenzymes involved in the 2-hydroxylation of oestradiol and 17α-ethinylestradiol. Biochem J 1990; 267: 221-6
108. Cavanaugh JH, Locke C, Karol M. Lack of interaction of lansoprazole or omeprazole with prednisone [abstract]. Am J Gastroenterol 1993; 88: 1589
109. Naidu MUR, Shobha JC, Dixit VK, et al. Effect of multiple dose omeprazole on the pharmacokinetics of carbamazepine. Drug Invest 1994; 7: 8-12
110. Kerr BM, Thummel KE, Wurden CJ, et al. Human liver carbamazepine metabolism, role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. Biochem Pharmacol 1994; 47: 1969-79
111. Böttiger Y, Bertilsson L. No effect on plasma carbamazepine concentration with concomitant omeprazole treatment. Clin Drug Invest 1995; 9: 180-1
112. Rost KL, Brösicke H, Heinemeyer G, et al. Specific and dose-dependent enzyme induction by omeprazole in human beings. Hepatology 1994; 20: 1204-12
113. Reill L, Erhardt F, Fischer R, et al. Effect of oral pantoprazole on 24-h intragastric pH, serum gastrin profile and drug metabolizing enzyme activity in man – a placebo-controlled comparison with ranitidine [abstract]. Gut 1993; 34 Suppl.: 63
114. Clark DWJ. Genetically determined variability in acetylation and oxidation. Drugs 1985; 29: 342-75
115. Gustavson LE, Kaiser JF, Edmonds AL, et al. Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. Antimicrob Agents Chemother 1995; 39: 2078-83

Correspondence and reprints: Dr *Peter Unge*, Department of Medicine, Sandviken Hospital, S-811 89 Sandviken, Sweden.