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Omeprazole: Pharmacology, Pharmacokinetics and Interactions

B. Oosterhuis, J.H.G. Jonkman

Pharma Bio-Research International BV, Assen, The Netherlands

Key Words. Omeprazole · Pharmacology · H^+-K^+-ATPase · Pharmacokinetics · Interaction · Cytochrome P-450 · Drug metabolism

Abstract. Omeprazole is a prodrug which is converted to its active form only at the site of action, namely the parietal cell. There it binds irreversibly with H^+-K^+-ATPase (the gastric proton pump), which causes an effective and long-lasting inhibition of gastric acid secretion. The pharmacokinetic profile of omeprazole is rather complicated, showing concentration-dependent elimination kinetics and an oral bioavailability which increases with the dose and during repeated administration. For the choice of dosage regimens this has minor consequences, in view of the wide therapeutic range of omeprazole and because an almost continuous maximum effect is obtained with once daily oral administration of 20–40 mg. Omeprazole may influence the pharmacokinetics of concurrently administered drugs by an inhibition of their oxidative metabolism. For most drugs studied thus far, the influence is less or even negligible in comparison with the influence of cimetidine, with the exception of diazepam. For every new combination of omeprazole with a drug that has a critical therapeutic range the consequences of a possible interaction should be studied.

Introduction

The history of the development of omeprazole gives an illustration of how important discoveries often occur by coincidence. On the other hand, it illustrates how an increase of knowledge on biochemistry and physiology greatly benefits the rational development of drugs. For omeprazole the history goes back to 1966 [1]. Scientists at Hässle are trying to find a local anaesthetic which retains its action in an acidic environment. In 1972 compounds without local anaesthetic properties, but with a pronounced antisecretory effect in the rat are found. In 1973 and 1974 a number of substituted benzimidazoles are synthesised which are already structurally related to omeprazole. In 1973, the gastric proton pump, H^+-K^+-ATPase is discovered [2] as the en-

zyme that is responsible for acid secretion in the gastric mucosa. At Hässle one finds in 1979 that the benzimidazole derivatives are specific inhibitors of this gastric proton pump. This knowledge improves the possibility to work in a rational way and leads to the selection of omeprazole as the optimal structure (fig. 1). The molecule contains a substituted benzimidazole and a substituted pyridine ring connected to each other via a sulfoxide-containing chain. From a biopharmaceutical point of view it is important that the compound is an ampholyte, being both a weak acid and a weak base. Under neutral conditions the compound is not ionized and hardly soluble in water. The compound is not very stable and decomposes rapidly in acidic aqueous solutions.

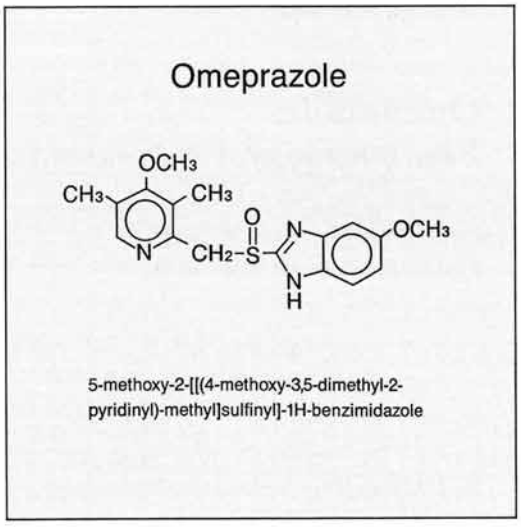


Fig. 1. Chemical structure of omeprazole.

Pharmacology of Omeprazole

Physiology of Gastric Acid Secretion

For some understanding concerning the mechanism of action of omeprazole, it is necessary to briefly discuss the physiology of gastric acid secretion [3]. This occurs in specific secretory cells, the parietal cells, which are located in the gastric mucosa. The secretory surfaces of these parietal cells are deeply invaginated to form channels (cannaliculi) which are in open contact with the stomach lumen. A schematic and very simplified depiction of the parietal cell and its physiology is given in figure 2. Primarily, K^+ and Cl^- are secreted to the cannaliculi. Subsequently, K^+ is exchanged against H^+ by H^+-K^+-ATPase, the proton pump which is located in the secretory membrane. As a result the pH in the cannaliculi becomes very low (less than pH 1). The energy required for that process is provided by ATP. The activity of the proton pump is regulated by cholinergic, histaminergic and gastrinergic stimulation, with Ca^{2+} or cAMP as secondary messengers. At this stage the H_2-receptor antagonists (cimetidine, ranitidine) block the stimulation by histamine, and antimuscarinic drugs (pirenzepine) block the stimulation by acetylcholine.

Mechanism of Action of Omeprazole

On the basis of many in vitro and in vivo studies with omeprazole the following model has been accepted for the events leading to inhibition of gastric acid production [3]. Omeprazole in the intact form enters the parietal cell from the serosal side. When it enters the cannaliculi, it is protonated and accumulated. Subsequently, the pronated form of omeprazole decomposes into an active form, which reacts with H^+-K^+-ATPase and causes an irreversible inactivation of the enzyme. This means that omeprazole is in

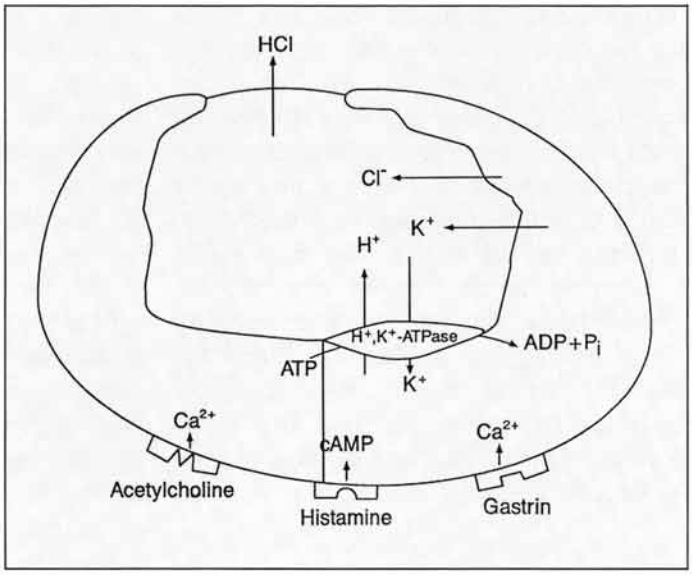


Fig. 2. Acid production by the parietal cell. Schematic depiction of the parietal cell and its physiology.

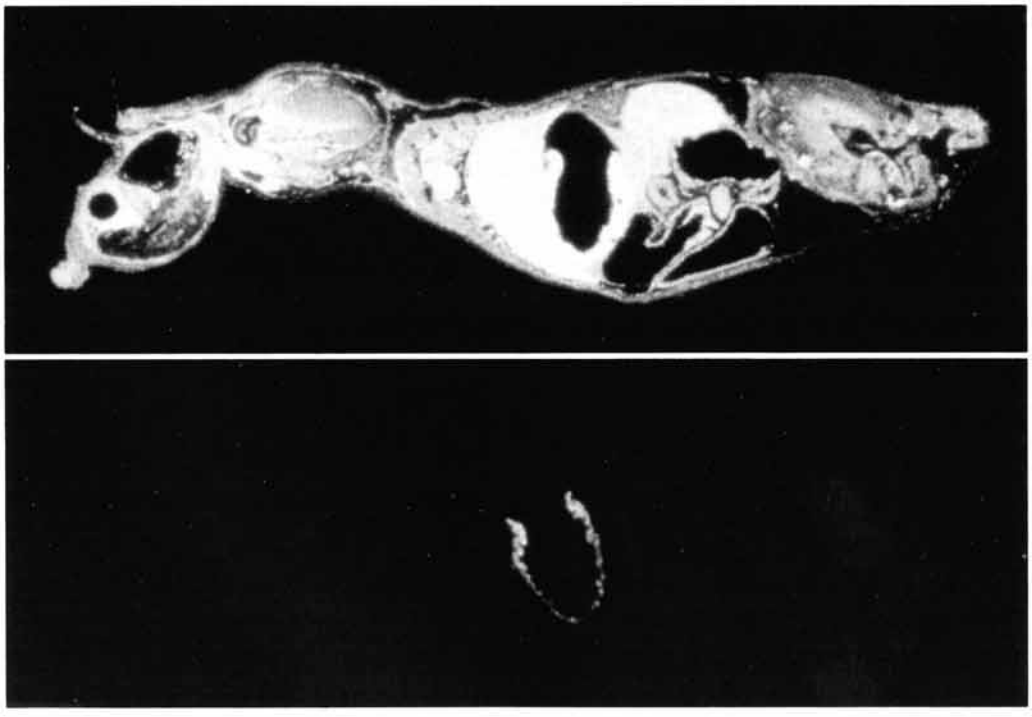


Fig. 3. Autoradiograms showing the distribution of radioactivity (light area) in a mouse 1 min (**a**) and 16 h (**b**) after intravenous injection of ^{14}C-omeprazole. From Helander et al. [4].

fact an inactive prodrug, which is accumulated at the site of action, and only there is it converted to its active form. This is a perfect example of drug targeting. The selective affinity of the active form of omeprazole for the gastric mucosa has been supported by results of autoradiography. A striking illustration is provided by results from whole body autoradiography in the mouse (fig. 3). The sagittal section at 1 min after injection of ^{14}C-labelled omeprazole shows that the isotope is present mainly in the liver, the lungs and the kidneys. At 16 h after injection, high levels of the isotope are seen only in the gastric wall [4].

Pharmacokinetics and Pharmacodynamics of Omeprazole

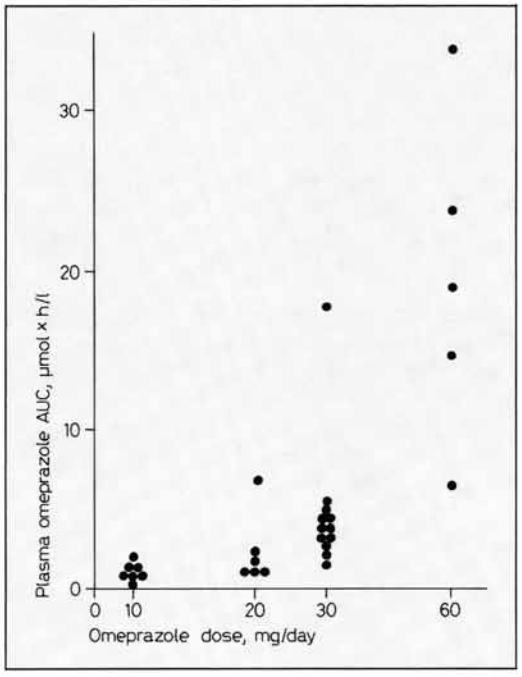
Pharmacokinetics

After intravenous administration omeprazole plasma concentrations decline bioexponentially. The apparent volume of distribution is about 0.3–0.4 litres·kg^{-1}, which is compatible with localization of the drug in extracellular water. Plasma protein binding is between 95 and 96% in human plasma. Omeprazole is eliminated rapidly (with a half-life of about 1 h) and almost completely by metabolism. The total plasma clearance is about 40 litres·kg^{-1} [5].

Three metabolites of omeprazole have been identified in human plasma, namely hydroxyomeprazole, omeprazole sulfone and omeprazole sulphide [6]. None of these is considered to contribute to the antisecretory effect [5]. The results of several studies suggest that omeprazole shows to some extent dose-dependent kinetics. The AUC increases more than proportional with dose, $t_{½}$ is longer and the clearance is smaller with higher doses. This becomes particularly significant when the dose is increased above 40 mg [7; Oosterhuis et al., unpubl. results]. A possible explanation is that the capacity for metabolic elimination is limited and becomes saturated at higher omeprazole plasma concentrations.

A complicating factor in oral administration is the rapid decomposition of omeprazole at the pH in the stomach. This problem is circumvented with the marketed oral formulation. The capsules contain enteric-coated granules, which only release the active substance in a neutral to alkaline environment. The oral bioavailability of omeprazole appears to increase during repeated once daily administration. It has been suggested that omeprazole may increase its own relative bioavailability by increasing the pH in the stomach [8].

The absolute bioavailability of single doses of various formulations of omeprazole was also found to depend on the dose. Regårdh et al. [7] reported that the mean systemic availability of a buffered oral solution of omeprazole increased with dosage, being 40.3, 53.6, 58.2 and 96.9% with doses of 10, 20, 40 and 90 mg, respectively. Saturation of first-pass metabolism at higher doses was suggested as a reason for this increase. As a consequence, the disproportional increase of AUC with the dose after oral administration is even more pronounced than after i.v. administration of omeprazole. This is, for instance, illustrated by the results from a study by Pounder et al. [9] as shown in figure 4. The omeprazole AUC was measured after the last dose of a treatment with different omeprazole doses once daily during at least 7 days. Particularly above 20 mg there was a more than proportional increase of AUC with dose.



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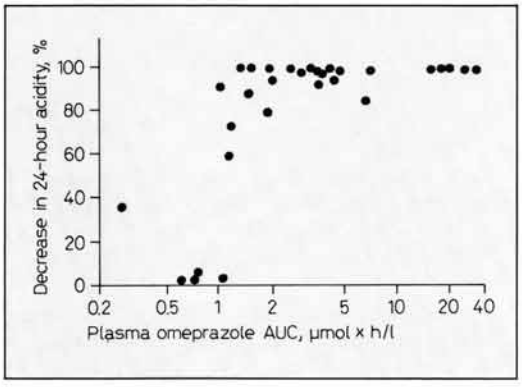

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Fig. 4. Area under plasma omeprazole concentration-time curve (AUC) as function of the oral dose. From Pounder et al. [9].

Fig. 5. Percentage decrease of mean 24-hour intragastric acidity as function of omeprazole AUC. From Pounder et al. [9].

Pharmacodynamics

As omeprazole is in fact a prodrug, and in view of the irreversible nature of the effect, it is not surprising that the results of many studies indicate only a remote concentration-effect relationship. This relationship was also investigated in the aforementioned study of Pounder et al. [9].

Figure 5 shows the correlation of the antisecretory effect over 24 h with omeprazole AUC. The 24-hour acidity was calculated as the average of H^+ activities as measured in gastric contents at hourly intervals during 24 h after the same doses for which the omeprazole AUC was measured. When the AUC was below 1 $\mu mol \cdot h^{-1}$ there was hardly any effect, but when the AUC increased above 1 $\mu mol \cdot h^{-1}$, the effect became maximal almost immediately. The latter indicates some relationship between AUC and the overall effect on gastric acid secretion by omeprazole. On the other hand, there is no direct relationship between the omeprazole plasma concentration, and the antisecretory effect. Figure 6 shows gastric H^+ activity versus time plots from the study of Pounder et al. [9]. The last omeprazole dose was administered at 09.00 a.m. Although omeprazole was almost completely eliminated from plasma within 3 h, the mean effect lasted for at least 24 h, even for the 10-mg/day dose level. In the same study it was found that 1 week after cessation of 14 days' treatment with omeprazole 30–60 mg/day, the mean 24-hour gastric H^+ activity was still significantly reduced with respect to pretreatment values. Eight weeks after stopping omeprazole, the mean 24-hour gastric H^+ activity had returned to the pretreatment level.

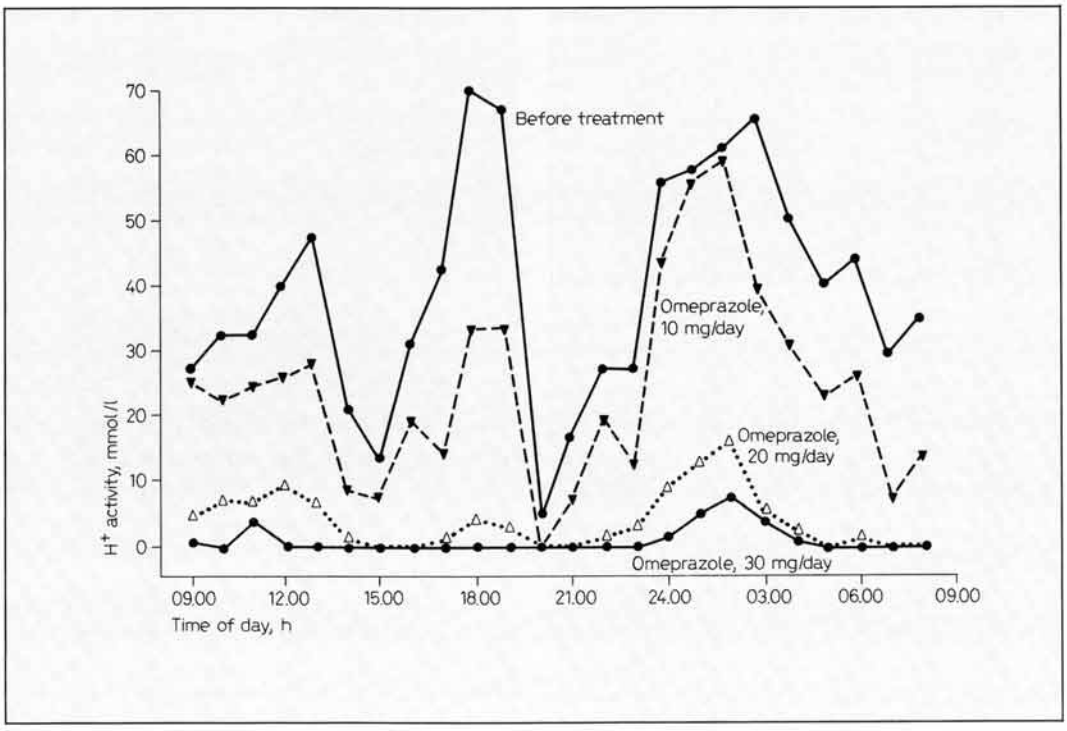

Fig. 6. Mean intragastric H^+ activity in 6 patients before and during treatment with omeprazole, 10, 20 or 30 mg once daily. The seventh dose was taken at 09.00 a.m. From Pounder et al. [9].

Pharmacokinetic Interactions with Omeprazole

From an early stage in the development of omeprazole the possibility of pharmacokinetic interactions with other drugs has been the subject of several animal (both in vitro and in vivo) and human investigations. In part, this may be due to the fact that omeprazole has a similar therapeutic indication as cimetidine, which has a distinct reputation with respect to pharmacokinetic interactions [10]. More importantly, the structures of both compounds include the imidazole ring, which is considered to be responsible for the inhibition of cytochrome P-450 enzymes.

Therefore, studies thus far have mainly focussed on the possible influence of omeprazole on the oxidative metabolism of other drugs. Results from in vitro studies on cytochrome P-450-mediated reactions have indicated that omeprazole more or less inhibits the metabolism of diazepam [11], 7-ethoxycoumarin [12], aniline [13], and antipyrine [14]. In table 1, a comparative survey is given of drug interactions with omeprazole and cimetidine as observed during clinical studies with patients or healthy volunteers. In general, the interactive effects of omepra-

Table 1. Interactions of omeprazole and cimetidine with concomitantly administered drugs by interference with oxidative metabolism

Drug Co-treatment	% change in				Reference
	$t_{½}$	Cl	V_d	AUC	
Theophylline					
Omeprazole					
40 and 80 mg i.v.	< 5	< 5		< 5	Oosterhuis et al., 1987
Cimetidine					
1,200 mg/day, 2 days	+73	−39			Jackson et al. [15], 1981
1,000 mg/day, 9 days	+37	−21			Roberts et al. [16], 1981
Antipyrine					
Omeprazole					
30 mg/day, 14 days	< 5	< 5	< 5		Henry et al. [17], 1984
60 mg/day, 14 days	+10	−14	< 5		Henry et al. [17], 1984
Cimetidine					
1,000 mg/day, 7 days		−26			Staiger et al. [18], 1981
Diazepam					
Omeprazole					
40 mg/day, 7 days	+130	−54	< 5		Gugler and Jensen [19], 1985
Cimetidine					
1,000 mg/day	+53	−43			Klotz and Reimann [20], 1980
1,200 mg/day	+34	−50		+76	Gough et al. [21], 1982
Fenytoin					
Omeprazole					
40 mg/day, 8 days	+27	−15	< 5		Gugler and Jensen [19], 1985
Cimetidine					
1,000 mg/day	< 5	−15	< 5		Frigo et al. [22], 1983
1,200 mg/day, 8 days				+71	Iteogu et al. [23], 1983
Propranolol					
Omeprazole					
20 mg/day, 8 days	< +5	< −10		< 5	Henry et al. [24], 1987
Cimetidine					
1,000 mg/day		−50		+94	Reimann et al. [25], 1981
Warfarine					
Omeprazole					
20 mg/day, 14 days				< 5	Sutfin et al. [26], 1988
Cimetidine					
1,000 mg/day		−36			Desmond et al. [27], 1984

zole appear to be minor at clinically relevant doses. The small interaction of omeprazole with warfarin was stereoselective. Omeprazole caused a slight decrease of the S (+) enantiomer and a small (12%) but significant increase of the less active R (–) enantiomer in plasma.

The anticoagulation activity was also measured in this study, and suggested that the interaction was of no clinical importance [26]. Inspection of the results in table 1 indicates that there is a pronounced discrepancy between the relative influence of omeprazole and cimetidine on the metabolism of various drugs. For theophylline and antipyrine, which are considered as model substrates to study changes in drug metabolism, the influence of omeprazole is much less in comparison with cimetidine. On the other hand, omeprazole produced considerably larger changes in diazepam disposition. A tentative conclusion could be that omeprazole inhibits different, and probably less, iso-enzymes of the cytochrome P-450 system than cimetidine.

As omeprazole has a pronounced influence on gastric pH it could also influence the absorption of concurrently administered drugs. In this respect it is reasonable to expect some correlation with the influence of other antisecretory drugs like cimetidine [10]. For omeprazole, the only study which focussed on this mechanism thus far concerned the interaction with digoxin [Oosterhuis et al., unpubl. results]. The disposition of an oral dose of digoxin (1 mg) was compared with and without pretreatment with omeprazole (20 mg/day during 11 days). Only minor changes were observed in the disposition of digoxin. On average, AUC from 0 to 96 h after digoxin administration showed a 10% increase ($p < 0.05$).

Concluding Remarks

Omeprazole is a prodrug which is converted to its active form only at the site of action, namely the parietal cell. There it causes an effective and long-lasting inhibition of gastric acid secretion.

The pharmacokinetic profile of omeprazole is rather complicated, showing concentration-dependent elimination kinetics, and an oral bioavailability which increases with the dose and during repeated administration. However, in view of the wide therapeutic range and the long-lasting effect, this has hardly consequences for the choice of dosage regimens. With once daily oral administration of 20–40 mg an almost continuous maximum effect is obtained.

Omeprazole may influence the pharmacokinetics of concurrently administered drugs by an inhibition of their oxidative metabolism. For most drugs studied thus far, the influence is less or even negligible in comparison with the influence of cimetidine, with the exception of diazepam. For every new combination of omeprazole with a drug that has a critical therapeutic range the consequences of a possible interaction should be studied.

References

1 Brandström A, Lindberg P, Junggren U: Structure activity relationships of substituted benzimidazoles. Scand J Gastroenterol 1985;20(suppl 108): 15–22.
2 Ganser A, Forte J: K^+-stimulated ATPase in purified microsomes of bullfrog oxyntic cells. Biochim Biophys Acta 1973;307:169–180.
3 Clissold S, Campoli-Richards M: Omeprazole. A preliminary review. Drugs 1986;32:1–47.
4 Helander H, Ramsay C-H, Regårdh C-G: Localization of omeprazole and metabolites in the

mouse. Scand J Gastroenterol 1985;20(suppl 108):95–104.
5 Regårdh C-G: Pharmacokinetics and metabolism of omeprazole in man. Scand J Gastroenterol 1986;21(suppl 118):99–104.
6 Lagerström P-O, Persson B-A: Determination of omeprazole and metabolites in plasma and urine by liquid chromatography. J Chromatogr 1984; 309:347–356.
7 Regårdh C-G, Gabrielsson M, Hoffman K-J, et al: Pharmacokinetics and metabolism of omeprazole in animals and man. An overview. Scand J Gastroenterol 1985;20(suppl 108):79–94.
8 Prichard P, Yeomans N, Mihaly G, et al: Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology 1985;88:64–69.
9 Pounder R, Sharma B, Walt R: Twenty-four hour intragastric acidity during treatment with oral omeprazole. Scand J Gastroenterol 1986;21(suppl 118):108–116.
10 Somogyi A, Muirhead M: Pharmacokinetic interactions of cimetidine 1987. Clin Pharmacokinet 1987;12:321–366.
11 Chenery R, Ayrton A, Oldham H, et al: The interaction of omeprazole with rat liver cytochrome P450-mediated mono oxygenase reactions in vitro and in vivo. Biochem Pharmacol 1988;37:1407–1414.
12 Jensen J, Gugler R: Inhibition of human liver cytochrome P450 by omeprazole. Br J Clin Pharmacol 1986;21:328–330.
13 Seitz H, Simanowski U, Simon B, et al: Effect of omeprazole on ethanol oxidation and aniline hydroxylation in rat hepatic microsomes. Z Gastroenterol 1988;26:188–190.
14 Webster L, Brian Jones D, Mihaly G, et al: Effect of omeprazole and PEG-400 on antipyrine elimination by the isolated perfused rat liver. J Pharm Pharmacol 1984;36:470–472.
15 Jackson J, Powell J, Wandell M, et al: Cimetidine decreases theophylline clearance. Am Rev Resp Dis 1981;123:615–617.
16 Roberts R, Grice J, Wood L, et al: Cimetidine impairs the elimination of theophylline and antipyrine. Gastroenterology 1981;81:19–21.
17 Henry D, Somerville K, Kitchingman G, et al: Omeprazole: effects on oxidative drug metabolism. Br J Clin Pharmacol 1984;18:195–200.
18 Staiger C, Männer C, Czygan P, et al: The influence of cimetidine on antipyrine pharmacokinetics in patients with and without cirrhosis of the liver. Int J Clin Pharmacol Ther Toxicol 1981;19: 561–564.
19 Gugler R, Jensen J: Omeprazole inhibits oxidative drug metabolism. Gastroenterology 1985;89: 1235–1241.
20 Klotz U, Reiman I: Delayed clearance of diazepam due to cimetidine. N Engl J Med 1980;302: 1012–1014.
21 Gough P, Curry S, Araujo O, et al: Influence of cimetidine on oral diazepam elimination with measurement of subsequent cognitive change. Br J Clin Pharmacol 1982;14:739–742.
22 Frigo G, Lecchini S, Caravaggi M, et al: Reduction in phenytoin clearance caused by cimetidine. Eur J Clin Pharmacol 1983;25:135–137.
23 Iteogu M, Murphy J, Shleifer N, et al: Effect of cimetidine on single-dose phenytoin kinetics. Clin Pharm 1983;2:302–303.
24 Henry D, Brent P, Whyte I, et al: Propranolol steady-state pharmacokinetics are unaltered by omeprazole. Eur J Clin Pharmacokinet 1987;33: 369–373.
25 Reimann I, Klotz U, Siems B, et al: Cimetidine increases steady state plasma levels of propanolol. Br J Clin Pharmacol 1981;12:785–790.
26 Sutfin T, Balmer K, Boström H, et al: Stereoselective interaction of omeprazole with warfarin in healthy men. Ther Drug Monit 1989, in press.
27 Desmond P, Mashford M, Harman P, et al: Decreased oral warfarin clearance after ranitidine and cimetidine. Clin Pharmacol Ther 1984;35: 338–341.

B. Oosterhuis
Pharma Bio-Research International BV
PO Box 147
9400 AC Assen (The Netherlands)