Omeprazole: Pharmacokinetics and Metabolism in Man

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Omeprazole is acid labile and, therefore, has to be protected from exposure to the acidic gastric juice when given orally. Following a single oral dose of buffered suspension, omeprazole is rapidly absorbed with peak plasma concentrations within 0.5 hours. The volume of distribution is 0.3 litres/kg corresponding to the volume of extracellular water. In contrast to the long duration of antisecretory action, omeprazole is rapidly eliminated from plasma. The half-life is less than 1 hour, and omeprazole is almost entirely cleared from plasma within 3–4 hours. Omeprazole is completely metabolized in the liver. The two major plasma metabolites are the sulphone and hydroxyomeprazole, neither of which contributes to the antisecretory activity. About 80% of a given dose is excreted in the urine, and the remainder via the bile. The absorption of the coated granule formulation dispensed in hard gelatine capsules is slower, with peak concentrations 1–3 hours after dose. Bioavailability after a single dose is 35% and increases during repeated once-daily dosing to 60%. Omeprazole can potentially interact with the hepatic microsomal cytochrome P-450 enzymes. Studies show that the clearance of both diazepam and phenytoin are decreased and their terminal half-lives are increased during concomitant omeprazole treatment, both interactions being attributable to inhibition of hepatic metabolism. No interaction with propranolol or theophylline has been noted.

Key words: Drug interactions; omeprazole; pharmacokinetics

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Omeprazole reduces gastric acid secretion in both animals and man by inhibiting the gastric proton (acid) pump (H^+,K^+-ATPase) in the secretory membrane of the parietal cell. The compound is, however, acid labile and has to be protected from exposure to acidic gastric juice when given orally. The solubility in water is very low. In early experimental studies in man, omeprazole was, therefore, administered as an oral suspension in a sodium bicarbonate solution, together with additional bicarbonate solution given at the same time (1). Omeprazole has been given intravenously, dissolved in a 40% polyethylene glycol 400/water solution (2). This solution, given with sodium bicarbonate to minimize acid degradation, has also been used for oral administration of ^{14}C-labelled omeprazole in many pharmacokinetic studies (3). These oral formulations were, however, unsuitable for clinical use, and omeprazole was subsequently formulated as enteric-coated granules (4). These granules were dispensed in ordinary hard gelatine capsules. This paper summarizes present knowledge of the pharmacokinetics and metabolism of omeprazole, with special reference to the relationship between plasma concentrations and effects on acid secretion.

PHARMACOKINETICS OF SINGLE DOSES

Omeprazole, given as a single oral dose in a buffered suspension or solution, is rapidly absorbed and peak plasma concentrations are achieved within 0.5 hours (1,5). After absorption, omeprazole is rapidly eliminated from the plasma with a terminal half-life of less than 1 hour. In most individuals, omeprazole is completely

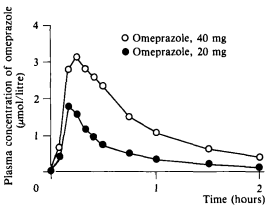

Fig. 1. Mean plasma omeprazole concentrations in 8 healthy subjects following a single oral dose of 20 or 40 mg as buffered suspension (data from Lind et al. (1)).

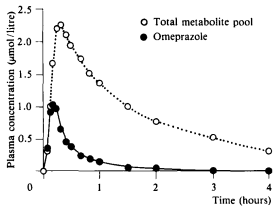

Fig. 2. Median plasma concentration-time curves for omeprazole and the total pool of radioactive metabolites in six healthy subjects following a single oral dose of ^{14}C-labelled omeprazole as a buffered solution (data from Regårdh et al. (3)).

cleared from the plasma within 3–4 hours (Fig. 1) (1). Studies with oral administration of ^{14}C-labelled omeprazole have shown that there is rapid and extensive formation of plasma metabolites (Fig. 2) (5). The plasma concentration-time curve for both omeprazole and the total pool of metabolites declined quickly indicating rapid elimination from the body; this is in contrast to the long duration of antisecretory action, which lasts for 3–4 days after a single dose (Fig. 3) (1, 3).

Thus, the degree of acid inhibition at any given time is independent of the plasma concentration of omeprazole or any of its metabolites. However, a significant correlation has been found between the degree of acid inhibition 2–4 hours after an oral dose and the area under the plasma

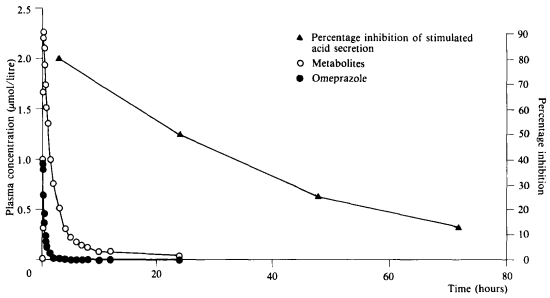

Fig. 3. Mean percentage inhibition of pentagastrin-induced acid secretion in six healthy subjects at various time points following a single oral dose of omeprazole, 20 mg, as buffered suspension (data from Lind *et al.* (1)) and median plasma concentration-time curves for omeprazole and the total pool of radioactive metabolites in six other healthy subjects following a single oral dose of ^{14}C-labelled omeprazole as a buffered solution (data from Regårdh et al. (3)).

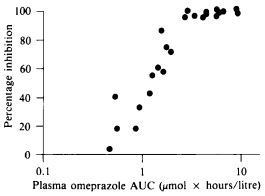

Fig. 4. Correlation between individual values for the area under the plasma omeprazole concentration-time curve (AUC) and percentage inhibition of pentagastrin-induced acid secretion 2–4 hours after various single oral doses of omeprazole buffered suspension in healthy subjects. Reproduced with permission from Lind et al. (1).

omeprazole concentration-time curve (AUC) (Fig. 4) (1). The omeprazole AUC reflects the product of the concentration of omeprazole in plasma and the time it is available in the systemic circulation and, therefore, available to the parietal cells.

Omeprazole is a lipophilic weak base. It is distributed into the parietal cells when available in the systemic circulation. Within the parietal cells omeprazole is concentrated in the acidic compartments because it is a weak base (6). In this acidic environment, omeprazole is protonated and chemically transformed to its active sulfenamide form, which binds and inactivates the proton transporting ATPase in the secretory membrane (6). The long-lasting binding of the active form of omeprazole to the H^+,K^+-ATPase in the parietal cells accounts for the lack of correlation between plasma concentration and degree of acid inhibition at any given time (6). Thus, the initial degree of acid reduction is dependent on the amount of drug available to the parietal cells, but the duration of acid inhibition is not dependent on sustained plasma concentrations.

METABOLISM AND ELIMINATION

After single oral and intravenous doses of ^{14}C-labelled omeprazole in young healthy subjects, about 80% of the radioactivity was detected in the urine and the remainder in the faeces (5). The amount recovered was similar for both routes of administration. No unchanged omeprazole was found in either the urine or the faeces. This suggests that omeprazole is completely metabolized before excretion. The bioavailability of the oral dose was about 50%, which indicates a fairly extensive first-pass metabolism.

The two main plasma metabolites in man have been identified as the sulphone and hydroxyomeprazole (Fig. 5) (5). The sulphone does not possess any antisecretory activity and hydroxyomeprazole is more than 100 times less potent than omeprazole (Wallmark B, personal communication). Some hydroxyomeprazole is excreted in the urine, but a fraction is probably further metabolized to the corresponding carboxylic acid, which has been identified in the urine (5). The sulphone, on the other hand, is only found in very small quantities in the urine and most seems to be further metabolized to more polar metabolites (5).

The biliary excretion of omeprazole has also been studied using intravenous administration of a very small (non-antisecretory) dose of radiolabelled omeprazole (7). During the first 4 hours, 16% of the given dose was recovered in the bile. As omeprazole is a weak base and, therefore, could be excreted via the acidic gastric juice, this route of excretion was also studied. However, negligible amounts (<1%) of the given dose were found in the gastric juice during the first 4 hours. It was concluded that the faecal recovery of omeprazole metabolites can be solely explained by biliary excretion and that this is the only important gastrointestinal route of elimination.

COMPARATIVE PHARMACOKINETICS

The pharmacokinetics of single oral and intravenous doses of radiolabelled omeprazole have been studied in different categories of patients (5,8). The mean plasma omeprazole concentration-time curves are shown in Fig. 6 and the pharmacokinetic variables summarized in Table I.

In patients with impaired renal function, the kinetics of unchanged omeprazole were essen-

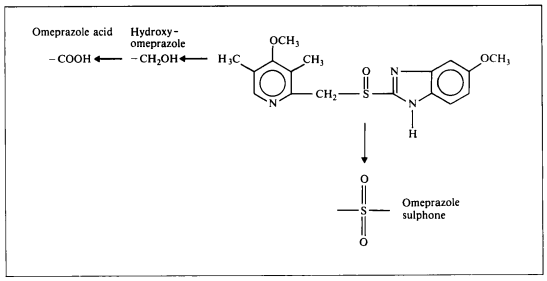

Fig. 5. Major metabolic pathways of omeprazole in man.

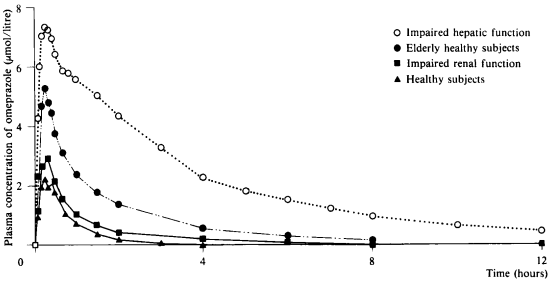

Fig. 6. Mean plasma concentration-time curves for omeprazole after a single oral dose of 40 mg, as a buffered solution in 18 young healthy subjects (3), 14 elderly healthy subjects (5), 12 patients with various degrees of renal function impairment (8), and 6 patients with various degrees of liver function impairment.

tially similar to those in healthy subjects. The rate of elimination of the total pool of metabolites was slower in these patients but, despite a marked reduction in kidney function, the elimination rate for the total pool of metabolites was such that no major accumulation is expected to occur during once-daily dosing (8). In elderly patients, the rate of elimination of omeprazole was on average slower and the bioavailability somewhat greater, while in patients with impaired hepatic function, the metabolism was considerably slower and the bioavailability close to 100%. It must be pointed

Table I. Pharmacokinetic variables for a single oral dose of omeprazole, 40 mg, in buffered solution and a single intravenous dose of omeprazole, 20 mg. Values are given as median with range. From the data referred to in Fig. 6

	Clearance (litres/minute)	Half-life (hours)	Vβ (litres/kg)	F
Young healthy subjects, n=18 (3)	0.62 (0.06–0.83)	0.50 (0.27–2.52)	0.32 (0.18–0.55)	0.46 (0.25–1.17)
Elderly healthy subjects, n=14 (5)	0.23 (0.08–0.48)	0.84 (0.49–2.00)	0.23 (0.22–0.34)	0.79 (0.33–1.14)
Patients with impaired hepatic function, n=8 (5)	0.07 (0.04–0.08)	2.68 (2.09–3.52)	0.20 (0.19–0.26)	0.98 (0.82–1.13)
Patients with impaired renal function, n=12 (8)	0.54 (0.27–0.93)	0.48 (0.34–0.93)	0.34 (0.27–0.48)	0.71 (0.10–1.24)

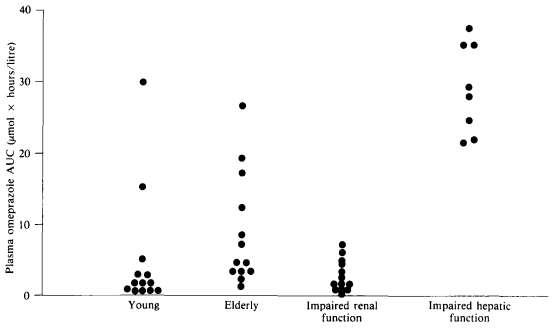

Fig. 7. Individual data for the area under the plasma omeprazole concentration-time curve (AUC) following a single oral dose of omeprazole, 40 mg, as a buffered solution. From the data referred to in Fig. 6.

out that the half-life of omeprazole in these patients was still as short as 2–4 hours. This suggests that the degree of general liver function impairment does not necessarily parallel the change in omeprazole metabolism, particularly as some young healthy subjects had similar half-lives and plasma AUCs (Fig. 7).

The most important pharmacokinetic variable for the degree of antisecretory effect of omeprazole seems to be the plasma concentration AUC with which it has a close relationship. The range of individual data for the omeprazole AUC (Fig. 7) in most subjects was similar in healthy subjects and patients with impaired renal function. In elderly patients, the AUC was on average higher, but there was a considerable overlap with the last two categories. Patients with impaired hepatic function had a consistently higher AUC than normal subjects.

Two healthy subjects had much higher AUC values than others in their group. Their AUC values were in the same range as those found in

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