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Clinical Pharmacology of Omeprazole

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Summary

Omeprazole is a specific inhibitor of H^+,K^+-ATPase or 'proton pump' in parietal cells. This enzyme is responsible for the final step in the process of acid secretion; omeprazole blocks acid secretion in response to all stimuli. Single doses produce dose-dependent inhibition with increasing effect over the first few days, reaching a maximum after about 5 days. Doses of omeprazole 20mg daily or greater are able to virtually abolish intragastric acidity in most individuals, although lower doses have a much more variable effect. Omeprazole causes a dose-dependent increase in gastrin levels.

Omeprazole must be protected from intragastric acid when given orally, and is therefore administered as encapsulated enteric-coated granules. Absorption can be erratic but is generally rapid, and initially the drug is widely distributed. It is highly protein-bound and extensively metabolised. Its elimination half-life is about 1h but its pharmacological effect lasts much longer, since it is preferentially concentrated in parietal cells where it forms a covalent linkage with H^+,K^+-ATPase, which it irreversibly inhibits. Omeprazole binds to hepatic cytochrome P450 and inhibits oxidative metabolism of some drugs, the most important being phenytoin.

Omeprazole has produced short term healing rates superior to the histamine H_2-receptor antagonists in duodenal ulcer, gastric ulcer and reflux oesophagitis. It has also been shown to be highly effective in healing ulcers which have failed to respond to H_2-receptor antagonists, and has been extremely valuable in treating patients with Zollinger-Ellison syndrome.

1. Chemistry and Pharmacology of Omeprazole

1.1 Chemistry

The molecular structure of omeprazole is composed of a substituted pyridine ring linked to a benzimidazole by a sulfoxide chain (fig. 1). Its molecular weight is 345 daltons. Omeprazole is a lipophilic weak base, and will therefore preferentially accumulate in an acidic environment such as the secretory membrane of the parietal cell.

1.2 Mode of Action

Omeprazole is avidly taken up by the parietal cell. In an acidic pH it becomes converted to its active form, a sulphenamide, by protonation. In this form, the drug produces an irreversible linkage via a disulfide bond with the enzyme H^+,K^+-ATPase or 'proton pump' (fig. 2) which is responsible for the active secretion of hydrogen ions by the parietal cells (Sachs & Wallmark 1989; Wallmark 1989) .

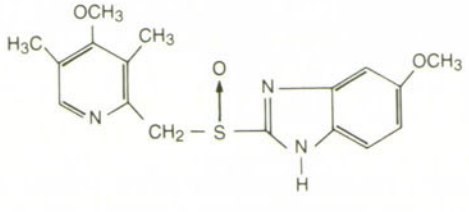

Fig. 1. Chemical structure of omeprazole.

This action makes omeprazole unique among existing gastric antisecretory drugs which are competitive antagonists at specific cellular receptors on the basolateral aspect of the parietal cell. Through its irreversible inhibition of H^+,K^+-ATPase, omeprazole blocks gastric acid secretion in response to all known stimuli including agents such as dibutryl cyclic adenosine monophosphate (db-cAMP), which acts intracellularly (Wolfe & Soll 1988).

Omeprazole is degraded by acid, and so must be protected from gastric acid when given orally; this is achieved by the use of encapsulated enteric-coated granules.

2. Pharmacodynamics in Humans

2.1 Effect on Basal Acid Output

Following oral administration of omeprazole in its encapsulated enteric-coated granule formulation, its maximal effect on gastric acid secretion is

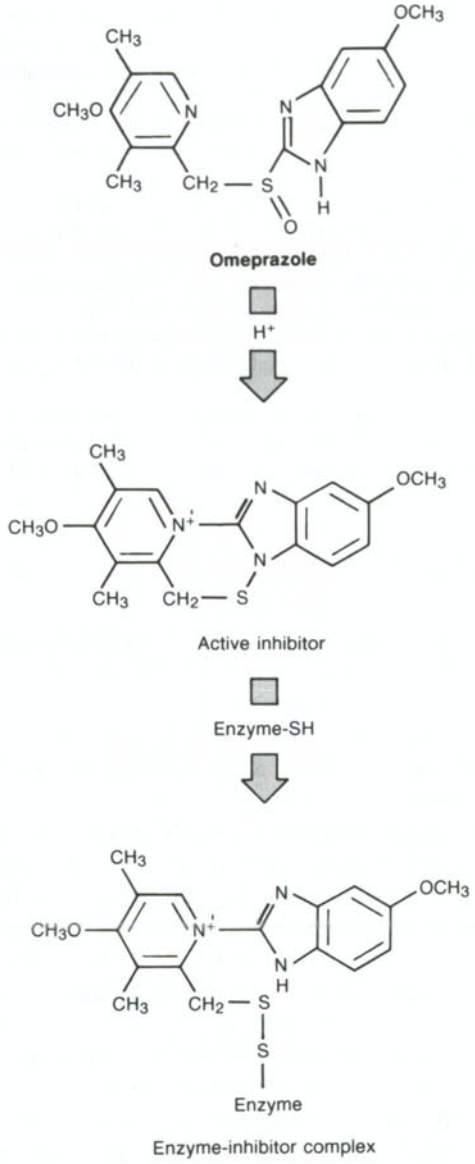

Fig. 2. Diagram of the interaction of the activated form of omeprazole with gastric H^+,K^+-ATPase.

achieved after about 6 hours: in a group of 6 healthy male subjects given omeprazole 30mg, basal acid output measured 6 hours later was reduced by 66% (Howden et al. 1984a). After 1 week of daily administration of the same dose, the inhibition of basal acid output had risen to almost 100%. In a similar group of 6 subjects given omeprazole 60mg daily, inhibition of basal acid output was 91.7% after the first dose and 99.1% after the seventh.

In a separate study, the effects of 7 days' administration of omeprazole 10mg daily were assessed (Howden et al. 1985a). A single dose of 10mg did not significantly affect basal acid output, but after 7 days of dosing mean basal acid output was reduced by 93%. However, there was a high degree of interindividual variability in response to this low dose.

These studies show a dose-dependent effect of omeprazole on inhibition of basal acid output. They also show variability in response to low dose omeprazole, and increased antisecretory effect with repeated dosing.

2.2 Effect on Pentagastrin-Stimulated Acid Output

Intravenous infusion of pentagastrin 1.2 μg/kg for 1 hour increased gastric acid secretion in a group of 6 healthy male subjects from a mean (± SD) basal value of 4.3 ± 3.4 mmol/h to a plateau value of 35.4 ± 5.4 mmol/h (Howden et al. 1984a). Omeprazole 30mg reduced the pentagastrin-stimulated plateau acid output to 10.2 ± 10.1 mmol/h (−71.2%; $p < 0.05$). After 7 days of dosing with omeprazole 30mg daily, this was further reduced to 0.6 ± 1.0 mmol/h (−98.4%; $p < 0.01$).

In subjects given omeprazole 60mg daily, pretreatment plateau acid output was 37.1 ± 10.6 mmol/h. After 1 dose this was reduced to 1.7 ± 2.3 mmol/h (−95.3%; $p < 0.01$); after the seventh dose, it was 0.4 ± 0.2 mmol/h (−99%; $p < 0.01$). In subjects given omeprazole 10mg daily (Howden et al. 1985a), pretreatment plateau acid output was 23.3 ± 8.2 mmol/h. Six hours after a single dose of 10mg, the figure was 23.1 ± 8.6 mmol/h (not significant) but at a similar time after the seventh daily dose it was 7.8 ± 6.7 mmol/h (−66.5%; $p < 0.01$). Again, there was a high degree of interindividual variability in response to the low dose.

In a group of patients with healed duodenal ulcer, pentagastrin-stimulated acid output after 7 days of dosing with placebo or omeprazole 5 or

10mg daily was measured 14 hours after the final dose (Howden et al. 1986a). Total output was 42.9 ± 4.9 mmol following placebo, and 34.5 ± 9.8 and 32.3 ± 8.7 following omeprazole 5 and 10mg, respectively. Neither of the reductions in output produced by these low doses of omeprazole was significant.

2.3 Effect on Insulin-Stimulated Acid Output

Omeprazole 30mg as a single oral dose reduced the stimulated acid output induced by an intravenous infusion of insulin 0.03 U/kg/h (Utley et al. 1985) from 16.8 ± 2.2 to 4.3 ± 1.8 mmol/h (−74%; $p < 0.05$). A similar group of subjects received a single dose of omeprazole 60mg, and in this group the insulin-stimulated acid output was reduced from 12.3 ± 2.6 to 3.4 ± 2.1 mmol/h (−73%; $p < 0.05$).

2.4 Effect on 24-Hour Intragastric Acidity

In a group of 9 patients with duodenal ulcer in clinical remission, a regimen of omeprazole 30mg daily for 1 week virtually eliminated intragastric acidity, with mean hourly hydrogen ion activity falling from 38.5 to 1.95 mmol/L (Walt et al. 1983). The median intragastric pH rose from 1.4 to 5.3, representing a much greater increase than that achieved by conventional doses of existing histamine H_2-receptor antagonists.

In another study, 12 duodenal ulcer patients received omeprazole 20mg daily for 28 days (Lanzon-Miller et al. 1987). At the end of that time, median integrated 24-hour intragastric acidity had fallen from 1148 to 36 mmol/L • h (−97%). The same patients also received a separate course of treatment with ranitidine 150mg twice daily; the median integrated 24-hour intragastric acidity with that treatment was 490 mmol/L • h (−57% compared with pretreatment values).

Omeprazole 20mg daily for 8 days reduced intragastric acidity by around 99% in 6 patients with healed duodenal ulcer (Naesdal et al. 1987) but had a much smaller effect on another 4 patients in the same study, indicating some degree of interindividual variability in response to this dose.

Finally, a dosage regimen of omeprazole 5 or 10mg daily for 7 days did not have any significant effect on 24-hour intragastric acidity in a group of 6 patients with healed duodenal ulcer (Howden et al. 1986a).

2.5 Effect on Plasma Gastrin Levels

Plasma concentrations of a wide variety of gastrointestinal peptides were measured in 6 healthy subjects 6 hours after a single oral dose of omeprazole 40mg (Allen et al. 1984). The basal level of gastrin was significantly ($p < 0.05$) increased from 13 ± 6.8 to 28.2 ± 8.3 pmol/L. The integrated gastrin response to a meal was also increased, but failed to reach statistical significance. No significant changes were found in the concentrations of any of the other peptides measured.

In a group of 12 healthy volunteers given omeprazole 40mg daily for 9 days by Festen et al. (1986), fasting serum gastrin levels increased from 36 ± 3 to 49 ± 6 ng/L ($p < 0.01$) after the first dose and to 59 ± 6 ng/L after the ninth ($p < 0.002$).

A nonsignificant increase in serum gastrin levels was found in 1 study of 10 duodenal ulcer patients given omeprazole 20mg daily for 8 days (Naesdal et al. 1987). Omeprazole 5 or 10mg daily for 7 days also produced no alteration in fasting gastrin levels in a group of 6 duodenal ulcer patients (Howden et al. 1986a). However, the median integrated gastrin response to a meal was significantly increased from 29.2 to 67.0 pmol/L • h ($p < 0.05$) following 7 days of omeprazole 10mg daily.

The median integrated 24-hour plasma gastrin was significantly raised from 328 to 1519 pmol/L • h in a group of 12 duodenal ulcer patients given omeprazole 20mg daily for 28 days (Lanzon-Miller et al. 1987). The median integrated 2-hour plasma gastrin for the same group of patients given ranitidine 150mg twice daily for 28 days was 799 pmol/L • h.

Omeprazole produces a dose-dependent increase in gastrin levels. The rise in integrated 24-hour gastrin is directly proportional to the reduc-

tion in integrated 24-hour intragastric acidity (Lanzon-Miller & Pounder, personal communication).

2.6 Effect on Pepsin Secretion

Although omeprazole has a dramatic effect on secretion of gastric acid, it does not significantly affect that of pepsin. Such a finding is consistent with the specific action of the drug on parietal cells without an effect on the function of the pepsin-secreting chief cells.

Thompson et al. (1985) found no significant alteration in pepsin output after 4 weeks of omeprazole 20 or 40mg daily in 9 patients with duodenal ulcer disease. Omeprazole 10mg daily for 7 days did not affect basal or pentagastrin-stimulated pepsin in 6 healthy volunteers (Howden et al. 1985a), and a higher dosage of 30 or 60mg daily for 7 days did not affect basal pepsin secretion in healthy volunteers (Howden et al. 1984a). Similarly, 12 healthy subjects given omeprazole 40mg daily for 9 days did not display any alteration in pentagastrin-stimulated pepsin output (Festen et al. 1986).

2.7 Effect on Intragastric Bacteria and Bacterial Products

Ten healthy male subjects were given omeprazole 30mg daily for 2 weeks in the study of Sharma et al. (1984). Gastric juice sampled 22 hours after the final dose of omeprazole showed a significant ($p < 0.01$) rise in the concentrations of bacteria, nitrite and *N*-nitrosamines and a nonsignificant reduction in nitrate levels. The profound inhibition of gastric acidity had allowed proliferation of intragastric bacteria with consequent reduction of dietary nitrate to nitrite and the production of *N*-nitrosamines. All these changes had resolved within 3 days of stopping omeprazole.

2.8 Effects on Endocrine Function

The effects of high dose endocrine function have been studied in healthy male subjects (Howden et al. 1986b; MacGilchrist et al. 1987). Omeprazole 60mg daily for 8 days had no effect on the basal levels of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin (PRL), thyroxine (T_4), triiodothyronine (T_3), cortisol or testosterone. In addition, the responses of TSH and PRL to stimulation with thyrotrophin-releasing hormone and the responses of FSH and LH to stimulation with luteinising hormone–releasing hormone were unaffected by omeprazole.

An initial finding of a reduction in the peak cortisol level in response to stimulation with synthetic corticotrophin (ACTH) in a group of healthy male subjects receiving omeprazole 60mg daily for 8 days (Howden et al. 1986c) was not subsequently confirmed (MacGilchrist et al. 1987). However, *in vitro* studies using isolated bovine adrenocortical cells showed that incubation with omeprazole produces a marked dose-dependent inhibition of stimulated cortisol release (Howden et al. 1986c). This is unlikely to have any significance for the use of omeprazole in humans, since extremely high concentrations of omeprazole were necessary to produce the effect.

2.9 Effects on Renal Tubular Function

Omeprazole 60mg administered daily for 7 days did not affect 24-hour urinary electrolyte excretion or urinary acidification in response to oral ammonium chloride in a group of 8 healthy male subjects (Howden & Reid 1984).

3. Pharmacokinetics in Humans

3.1 Absorption and Serum Concentrations

Since omeprazole is acid-labile, it must be protected from the action of acidic gastric juice when given by mouth. In some studies, this was achieved by administering the drug with oral sodium bicarbonate (e.g. Cederberg et al. 1989). Absorption of omeprazole was rapid, with peak plasma concentrations being reached within 0.5h.

This drug is usually administered as encapsulated enteric-coated granules. The release from this formulation and subsequent absorption are erratic and do not follow classic pharmacokinetic princi-

ples. Studies have shown marked interindividual variability in both the rate and extent of absorption.

In most healthy male subjects given omeprazole 10, 30 or 60mg daily (Howden et al. 1984b, 1985a), peak plasma omeprazole concentrations were achieved by 1.5 hours, although there was marked variation in individual peak concentrations. The ranges were 58 to 154, 223 to 1160 and 860 to 3830 μg/L after single doses of 10, 30 and 60mg, respectively. The area under the plasma omeprazole/time curve from administration until 8 hours after the dose ($AUC_{(0-8)}$) calculated by the linear trapezoidal rule also showed marked interindividual variation: the ranges after single oral doses of 10, 30 and 60mg were 156 to 428, 338 to 2270 and 1380 to 5000 μg/L · h, respectively.

After 7 days of treatment with these doses administered daily, the $AUC_{(0-8)}$ had increased from that of the first dose (Howden et al. 1984b, 1985a); the mean increases were 45% after 10mg daily, 86% after 30mg daily and 128% after 60mg daily. This implies a degree of nonlinearity which has also been noted by others. In a group of healthy volunteers given omeprazole either 10, 20 or 40mg daily for 5 days, the increases in AUC from days 1 to 5 averaged 21, 69 and 182%, respectively (Andersson et al. 1989).

The most likely explanation for the observed rise in AUC is that omeprazole absorption increases with repeated dosing due to a progressive suppression of acid secretion. Less omeprazole is degraded once acid secretion is inhibited, leaving more available for absorption. The increase in AUC cannot be explained by decreased elimination, since the clearance of omeprazole does not change with continuous treatment (Ching et al. 1990).

The true bioavailability of omeprazole has been estimated at 35% after a single dose, increasing to approximately 60% following repeated daily doses (Cederberg et al. 1989). The time of administration does not materially influence its absorption. In 8 healthy male subjects given omeprazole 40mg daily for 5 days, the parameters of time to peak concentration, peak concentration and AUC were similar whether the doses had been taken at 0900 or 2100h each day (Prichard et al. 1985).

3.2 Distribution

Omeprazole is, initially, rapidly distributed to extravascular sites. The mean volume of distribution in 8 healthy volunteers given 20mg orally was reported by Regårdh et al. (1985) to be 0.31 L/kg, with a range of 0.19 to 0.45 L/kg. This would be compatible with localisation of the major fraction of omeprazole within extracellular water. Penetration of the drug into red blood cells is low, the ratio between whole blood concentrations and those in plasma being in the region of 0.6. Omeprazole is more than 95% bound to plasma proteins in humans, principally albumin and α_1-acid glycoprotein (Regårdh et al. 1985). It subsequently becomes preferentially concentrated within parietal cells.

3.3 Metabolism and Elimination

Omeprazole is almost entirely cleared by metabolism, so that virtually no unchanged drug is excreted (Clissold & Campoli-Richards 1986). After oral or intravenous administration of [^{14}C]-omeprazole, more than 80% of the radioactivity was recovered in the urine, with most of the remainder in the faeces. No unchanged drug was found in either urine or faeces (Cederberg et al. 1989; Regårdh 1986). The main metabolites in humans are the sulfone and hydroxy-omeprazole (fig. 3). The sulfone metabolite does not possess any antisecretory activity, while hydroxy-omeprazole is only weakly antisecretory (Cederberg et al. 1989).

After low dose omeprazole labelled with ^{14}C was given intravenously to volunteers, 16% was recovered in the bile within the first 4 hours (Lind et al. 1987). Negligible amounts of drug were recovered from gastric juice over this time, indicating that biliary excretion is the only important gastrointestinal route of elimination.

Elimination half-life after oral omeprazole has been estimated at about 1h (Cederberg et al. 1989; Regårdh et al. 1985). Omeprazole is almost entirely cleared from plasma at 4 hours after oral admin-

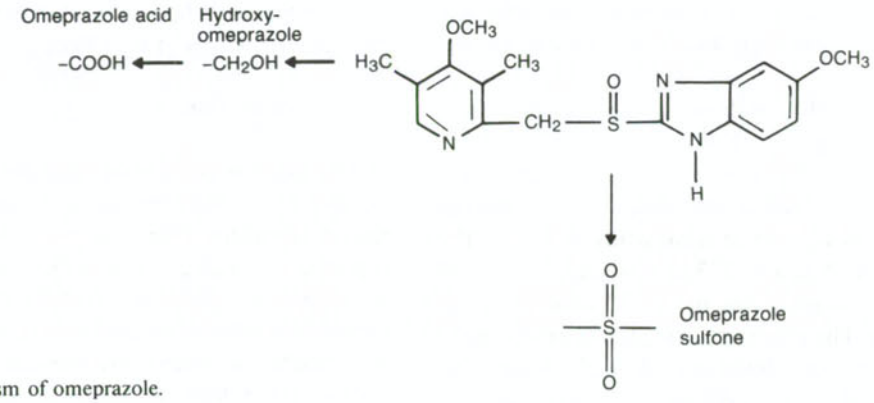

Fig. 3. Metabolism of omeprazole.

istration (Cederberg et al. 1989). The antisecretory effect of the drug, however, lasts much longer. Omeprazole becomes selectively concentrated in parietal cells (Cederberg et al. 1989; Wallmark 1989) where it acts as a noncompetitive inhibitor of H^+,K^+-ATPase. Suppression of acid secretion is not correlated with plasma omeprazole concentrations, but there is an association between omeprazole AUC and antisecretory effect (Cederberg et al. 1989; Lind et al. 1983).

3.4 Influence of Disease States on the Pharmacokinetics of Omeprazole

3.4.1 Chronic Renal Failure

The antisecretory effect of omeprazole is maintained in patients with chronic renal failure undergoing regular haemodialysis (Howden et al. 1985b). In 6 such patients given omeprazole 30mg by mouth, time to peak plasma concentration, peak plasma concentration and AUC did not differ between nondialysis and dialysis days. The drug was not detected in dialysis fluid. There was marked interindividual variability in these pharmacokinetic parameters. The range in AUC (138 to 3248 $\mu g/L \cdot h$) on the nondialysis day did not differ significantly from that in 6 healthy male subjects given a single oral dose of 30mg (338 to 2270 $\mu g/L \cdot h$: Howden et al. 1984b).

In the study by Naesdal et al. (1986), 12 patients with established chronic renal failure (creatinine clearance 11 to 62 ml/min) were given [^{14}C]-labelled omeprazole 20mg intravenously and 40mg orally in random order. The pharmacokinetics of omeprazole in these patients did not differ significantly from values previously found in healthy subjects. Mean elimination half-life was 0.6h, and mean systemic bioavailability was 70%.

3.4.2 Chronic Liver Disease

The oral and intravenous pharmacokinetics of omeprazole were studied in 10 patients with cirrhosis (McKee et al. 1988). Patients received omeprazole 10mg intravenously, and a 7-day course of 10mg orally. Acid secretion was low in these patients but omeprazole was still able to significantly reduce pentagastrin-stimulated acid output. The range of $AUC_{(0\text{-}8)}$ after the seventh oral dose was 3.97 to 10.61 $\mu mol/L \cdot h$, again indicating a high degree of intersubject variability. The AUCs were higher than those recorded in a group of healthy male subjects given omeprazole 10mg orally for 7 days (Howden et al. 1985a). The mean elimination half-life was 2.85h, which was higher than that reported for healthy subjects. There was no evidence of accumulation of omeprazole in the cirrhotic patients since no omeprazole was detectable in plasma at the start of the study on the seventh day of dosing. On the basis of these findings, specific dosage reduction is not necessary in patients with chronic liver disease. Doses of more than 20mg will not be needed in such patients.

Other researchers have reported mean values for elimination half-life of 2.68h (Cederberg et al. 1989) and 2.85h (Rondanelli et al. 1989) in cirrhotic patients.

4. Drug Interactions

Omeprazole can bind to hepatic cytochrome P450 and inhibit the oxidative metabolism of certain drugs. This section reviews drug-drug interactions reported in the literature.

4.1 Diazepam

Diazepam was the first drug reported to interact with omeprazole: Gugler and Jensen (1984) gave 8 healthy male subjects intravenous diazepam 0.1mg per kilogram of bodyweight before and after a 9-day course of omeprazole 40mg daily. Following omeprazole, the mean elimination half-life of diazepam was increased from 36.9 to 85.0h ($p < 0.01$) and the total body clearance was reduced from 1.34 to 0.61 L/h/kg ($p < 0.01$).

4.2 Aminophenazone (Aminopyrine) and Phenazone (Antipyrine)

Elimination of the 2 model drugs aminophenazone and phenazone was measured in a group of healthy male subjects given omeprazole 30 or 60mg daily for 2 weeks by Henry et al. (1984). The values for both drugs were not significantly altered in subjects receiving the lower dose. However, in 10 subjects given omeprazole 60mg daily, the half-life of aminophenazone was prolonged by 21% ($p < 0.05$) and that of phenazone by 10% ($p < 0.025$).

4.3 Phenytoin

In 8 healthy male subjects, the pharmacokinetics of phenytoin were studied before and after administration of omeprazole 40mg daily for 8 days (Gugler & Jensen 1985). The subjects were given phenytoin 250mg by intravenous infusion on each occasion. Phenytoin clearance was reduced from 0.025 to 0.021 L/h/kg after omeprazole ($p < 0.05$), and mean elimination half-life was increased from 20.7 to 26.3h ($p < 0.01$). The volume of distribution and protein binding of phenytoin were unaffected.

In a separate study (Prichard et al. 1987), 10 healthy male subjects received, in random order, placebo or omeprazole 40mg daily for 9 days. Phenytoin 300mg was given orally on the seventh day of each treatment. Phenytoin $AUC_{(0\text{-}72)}$ was significantly increased by omeprazole from 121.6 to 151.4 mg/L · h ($p < 0.01$), a finding which is of potential clinical importance in view of the narrow therapeutic index of phenytoin. There were non-significant increases in the peak plasma phenytoin concentrations and in the apparent elimination half-life.

4.4 Propranolol

Omeprazole 20mg daily for 8 days did not alter the pharmacokinetics of propranolol in a group of 8 healthy subjects taking propranolol 80mg twice daily (Henry et al. 1987).

4.5 Warfarin

A group of 21 healthy male subjects received warfarin for 7 weeks in doses adjusted to reduce vitamin K–dependent clotting factors to 10 to 20% of normal (Sutfin et al. 1989). For 2 weeks, they were also given omeprazole 20mg daily. Omeprazole did not affect plasma concentrations of the *S*-enantiomer of warfarin but caused a 12% increase in those of the *R*-enantiomer. Thrombotest values were slightly reduced during the concomitant administration, from a mean of 21.1% to 18.7% ($p = 0.04$). No adjustment in warfarin dosage was required. It appears that omeprazole inhibits the hepatic metabolism of the pharmacologically less active *R*-enantiomer of warfarin, but the effect was not great and is unlikely to be of major importance. Nevertheless, further studies are indicated.

4.6 Amoxycillin and Bacampicillin

The pharmacokinetics of oral amoxycillin 500mg and bacampicillin 800mg were studied in 8 healthy volunteers before and after 1 week of omeprazole

20mg daily (Paulsen et al. 1989). Although there was a slight delay in bacampicillin absorption, no significant effect was found on the AUC or elimination half-life of either amoxycillin or bacampicillin.

4.7 Nifedipine

In 10 healthy male volunteers, omeprazole 20mg administered daily for 7 days significantly ($p < 0.02$) reduced the clearance of nifedipine from 75 to 59.4 L/h (Danhof et al. 1989). Conversely, the clearance of omeprazole 40mg given intravenously was significantly reduced ($p < 0.03$) from 28.8 to 24.9 L/h in the same subjects when they had been pretreated with nifedipine 10mg 3 times daily for 5 days.

4.8 Antacids and Metoclopramide

Concomitant administration of antacids does not affect the absorption of omeprazole (Howden & Reid 1988; Tuynman et al. 1987). Similarly, there is no evidence for any interaction between omeprazole and metoclopramide (Howden & Reid 1988).

5. Therapeutic Uses of Omeprazole

5.1 Duodenal Ulcer

Duodenal ulcer healing rates for antisecretory drugs are directly related to their degree of suppression of 24-hour intragastric acidity (Jones et al. 1987). It is therefore not surprising that omeprazole has produced the highest recorded healing rates in duodenal ulceration. The first dose-comparative trial (Gustavsson et al. 1983) found a healing rate of 100% after 2 weeks of treatment with omeprazole 60mg daily in 16 patients. A similar group of 16 patients was given omeprazole 20mg daily; after 4 weeks, the healing rate was 93%.

Omeprazole has been shown to be superior to conventional doses of ranitidine in healing duodenal ulcers (Bardhan et al. 1986; Classen et al. 1985). However, a more recent multicentre clinical trial from Canada failed to demonstrate a statistically significant difference in healing rates between omeprazole 20mg daily and cimetidine in the high dose of 600mg twice daily (Archambault et al. 1988).

In an extensive meta-analysis of published clinical trials of antisecretory drugs in the treatment of duodenal ulcer (Jones et al. 1987), overall healing rates after 4 weeks of treatment with omeprazole 60, 40, 30 and 20mg were 100% ($n = 27$), 98.4% ($n = 126$), 92.8% ($n = 154$) and 95.5% ($n = 177$), respectively.

5.2 Gastric Ulcer

Omeprazole has been shown to be highly effective in healing benign gastric ulcers. In a detailed meta-analysis of published controlled trials of antisecretory drugs in gastric ulcer (Howden & Hunt 1990), omeprazole was associated with the highest overall healing rates. In addition, a significant relationship was demonstrated between gastric ulcer healing rates and percentage suppression of 24-hour intragastric acidity.

Walan et al. (1989) reported that in a large multicentre trial omeprazole 20 or 40mg once daily was superior to ranitidine 150mg twice daily in the treatment of ulcers of the body of the stomach or prepyloric ulcers. Omeprazole 20mg daily for 4 weeks healed 69% of gastric ulcers in 203 patients; a dosage of 40mg daily healed 80% of gastric ulcers in 194 patients at 4 weeks. In 205 patients given ranitidine 150mg twice daily, only 59% healed after the same period. Omeprazole was also shown to be highly effective in healing gastric ulcers in patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs). In patients who continued to take NSAIDs, 81% of ulcers healed within 8 weeks of concomitant therapy with omeprazole 40mg daily.

In a smaller study from Denmark (Danish Omeprazole Study Group 1989), omeprazole 30mg daily was compared with cimetidine 200mg 3 times daily and 400mg at night in 161 patients with gastric ulcers. Healing rates after 4 weeks were 77% in the omeprazole group and 58% in the cimetidine group. The 95% confidence interval of the difference between the 2 healing rates was from +4 to

+34%, indicating a real advantage for omeprazole. It was also shown that omeprazole was superior to cimetidine in healing large gastric ulcers.

5.3 Peptic Ulceration Refractory to Treatment

A high degree of efficacy has been shown for omeprazole in healing duodenal and gastric ulcers which have failed to respond to administration of H_2-receptor antagonists. In 18 patients with peptic ulcers refractory to prolonged therapy with these agents, treatment with omeprazole 40mg once daily led to satisfactory healing by 8 weeks in all patients (Tytgat et al. 1987).

Bardhan et al. (1988) studied a group of 107 patients whose ulcers had failed to heal despite daily treatment with cimetidine 1000mg or ranitidine 300mg. Patients were randomised either to continue on their H_2-receptor antagonist or to receive omeprazole 40mg daily: in the group receiving omeprazole 98% of ulcers had healed within 8 weeks, whereas the healing rate in patients continuing on H_2-receptor antagonists was 60%. The difference between the 2 treatments was highly significant ($p < 0.01$).

Brunner et al. (1988) studied the efficacy of omeprazole in patients with unhealed gastric or duodenal ulcers after treatment for more than 3 months with ranitidine 450 to 600mg daily. Of the patients with gastric ulcer, 41 of 43 healed within 8 weeks on treatment with omeprazole 40mg daily. In the patients with duodenal ulcer, all 11 healed within 4 weeks with omeprazole 40mg daily.

5.4 Reflux Oesophagitis

Omeprazole has been shown to be highly effective in treating the symptoms of reflux oesophagitis and in producing endoscopic healing of the lesions of oesophagitis. In the countries where omeprazole is currently licensed, reflux oesophagitis is recognised as one of its principal indications. Omeprazole has been shown to dramatically reduce oesophageal acid exposure in patients with this disease (Downton et al. 1987; Klinkenberg-Knol et al. 1988). Omeprazole does not affect lower oesophageal sphincter pressure (Dent et al. 1989; Downton et al. 1987), indicating that its efficacy in treating oesophagitis is due solely to its suppression of gastric acid secretion.

Omeprazole 20 or 40mg daily has been shown to be superior to placebo in healing reflux oesophagitis (Hetzel et al. 1988) with very little difference in healing rates between the 2 dose levels. Numerous trials have indicated that the drug is superior to H_2-receptor antagonists for this application (Blum et al. 1986; Havelund et al. 1988; Klinkenberg-Knol et al. 1987; Vantrappen et al. 1988; Zeitoun 1989). Omeprazole has also been shown to be particularly effective for treating the more severe grades of oesophagitis, where its superiority over the H_2-receptor antagonists is even more evident (Bate et al. 1989). Unfortunately, relapse of oesophagitis is very rapid after the drug is stopped (Dent et al. 1989): in 1 study (Hetzel et al. 1988), 82% of patients had relapsed within 6 months of stopping omeprazole. The question of long term maintenance treatment of these patients with the drug has not yet been adequately addressed.

One brief report (Deviere et al. 1989) suggests that omeprazole might induce regression of oesophageal columnar epithelium in patients with Barrett's oesophagus. This very interesting and potentially very important observation merits further study, and requires careful confirmation.

5.5 Zollinger-Ellison Syndrome

Initial case reports suggested that omeprazole might be of considerable value in the management of patients with Zollinger-Ellison syndrome (Blanchi et al.1982; Öberg & Lindström 1983). Subsequently, 2 series have confirmed this view. In the first (Lamers et al. 1984), 8 patients were studied after single and repeated dosing with omeprazole. Single doses of omeprazole 80mg adequately controlled the gastric hypersecretion in most patients, 7 of whom were adequately controlled by continued omeprazole use and had endoscopic healing of all peptic lesions after 4 weeks of treatment.

In a review of the first 80 patients with Zollinger-Ellison syndrome to receive omeprazole (Lloyd-Davies et al. 1988), excellent control of basal gastric acid secretion and of symptoms was demonstrated. The median dose of omeprazole required was 60 to 70mg daily, and over 90% of patients were satisfactorily managed on doses below 120mg daily. There was no tolerance or tachyphylaxis to continued omeprazole use, no further elevations in gastrin levels and no obvious drug-related effects on laboratory values.

References

Allen JM, Adrian TE, Webster J, Howe A, Bloom SR. Effect of single dose of omeprazole on the gastrointestinal peptide response to food. Hepato-gastroenterology 31: 44-46, 1984

Andersson T, Cederberg C, Heggelund A, Lundborg P. Omeprazole pharmacokinetics of single and repeated once daily administration of 10, 20 and 40mg as enteric coated granules. Abstract. European Journal of Clinical Pharmacology 36 (Suppl.): A142, 1989

Archambault AP, Pare P, Bailey RJ, Navert H, Williams CN, et al. Omeprazole (20mg daily) versus cimetidine (1200mg daily) in duodenal ulcer healing and pain relief. Gastroenterology 94: 1130-1134, 1988

Bardhan KD, Bianchi-Porro G, Bose K, Daly M, Hinchcliffe 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

Bardhan KD, Naesdal J, Bianchi-Porro G, Lazzaroni M, Hinchcliffe RFC, et al. Omeprazole in the treatment of refractory peptic ulcer. Abstract. Gastroenterology 94: A22, 1988

Bate CM, Keeling PWN, O'Morain CA, Wilkinson SP, Mountford RA, et al. Omeprazole provides faster healing and symptom relief of reflux oesophagitis than cimetidine. Abstract. Gut 302: A1493-A1494, 1989

Blanchi A, Delchier J-C, Soule J-C, Payen D, Bader J-P. Control of acute Zollinger-Ellison syndrome with intravenous omeprazole. Lancet 2: 1223-1224, 1982

Blum AL, Riecker EU, Dammann HG, Schiessel R, Lux G, et al. Comparison of omeprazole and ranitidine in the treatment of reflux esophagitis. New England Journal of Medicine 314: 716, 1986

Brunner G, Creutzfeldt W, Harke U, Lamberts R. Therapy with omeprazole in patients with peptic ulceration resistant to high-dose ranitidine treatment. Digestion 39: 80-90, 1988

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

Ching MS, Mihaly GW, Angus PW, Morgan DJ, Devenish-Meares S, et al. Oral bioavailability of omeprazole before and after chronic therapy in duodenal ulcer patients. British Journal of Clinical Pharmacology, in press, 1990

Classen M, Dammann H-G, Domschke W, Huttemann W, Londong W, et al. Omeprazole heals duodenal, but not gastric, ulcers more rapidly than ranitidine. Hepato-gastroenterology 32: 243-245, 1985

Clissold SP, Campoli-Richard DM. Omeprazole: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. Drugs 32: 15-47, 1986

Danhof M, Soons PA, van den Berg G, van Brummelen P, Jansen JBMJ, et al. Interactions between nifedipine and omeprazole. Abstract. European Journal of Clinical Pharmacology 36 (Suppl.): A258, 1989

Danish Omeprazole Study Group. Omeprazole and cimetidine in the treatment of ulcers of the body of the stomach: double-blind comparative trial. British Medical Journal 298: 645-647, 1989

Dent J, Hetzel DJ, Mackinnon MA, Reed WD, Narielvala FM. Evaluation of omeprazole in reflux oesophagitis. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 76-82, 1989

Deviere J, Buset M, Dumonceau J-M, Rickaert F, Cremer M. Regression of Barrett's epithelium with omeprazole. New England Journal of Medicine 320: 1497-1498, 1989

Downton J, Dent J, Heddle R, et al. Elevation of gastric pH heals peptic oesophagitis – a role for omeprazole. Journal of Gastroenterology and Hepatology 2: 317-324, 1987

Festen HPM, Tuynman HARE, Defize J, Frants RR, Straub JP, et al. Effect of single and repeated doses of oral omeprazole on gastric acid and pepsin secretion and fasting serum gastrin and serum pepsinogen I levels. Digestive Diseases and Sciences 31: 561-566, 1986

Gugler R, Jensen JC. Omeprazole inhibits elimination of diazepam. Lancet 1: 96, 1984

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

Gustavsson S, Adami H-O, Loof L, Nyberg A, Nyren O. Rapid healing of duodenal ulcers with omeprazole: double-blind dose-comparative trial. Lancet 2: 124-125, 1983

Havelund T, Laursen LS, Skoubo-Kristensen E, Andersen BN, Pedersen SA, et al. Omeprazole and ranitidine in treatment of reflux oesophagitis: double blind comparative trial. British Medical Journal 296: 89-92, 1988

Henry DA, Somerville KW, Kitchingham 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

Howden CW, Beastall GH, Reid JL. An investigation into the effects of omeprazole on renal tubular function and endocrine function in man. Scandinavian Journal of Gastroenterology 21 (Suppl. 118): 169-170, 1986b

Howden CW, Derodra JK, Burget DW, Hunt RH. Effects of low dose omeprazole on gastric secretion and plasma gastrin in patients with healed duodenal ulcer. Hepato-gastroenterology 33: 267-270, 1986a

Howden CW, Forrest JAH, Meredith PA, Reid JL. Antisecretory effect and oral pharmacokinetics following low dose omeprazole in man. British Journal of Clinical Pharmacology 20: 137-139, 1985a

Howden CW, Forrest JAH, Reid JL. Effects of single and repeated doses of omeprazole on gastric acid and pepsin secretion in man. Gut 25: 707-710, 1984a

Howden CW, Hunt RH. The relationship between suppression of acidity and gastric ulcer healing rates. Alimentary Pharmacology and Therapeutics 4, in press, 1990

Howden CW, Kenyon CJ, Beastall GH, Reid JL. Inhibition by omeprazole of adrenocortical response to ACTH: clinical studies and experiments on bovine adrenal cortex in vitro. Clinical Science 70: 99-102, 1986c

Howden CW, Meredith PA, Forrest JAH, Reid JL. Oral pharmacokinetics of omeprazole. European Journal of Clinical Pharmacology 26: 641-643, 1984b

Howden CW, Payton CD, Meredith PA, Hughes DMA, Macdougall AI, et al. Antisecretory effect and oral pharmacokinetics of omeprazole in patients with chronic renal failure. European Journal of Clinical Pharmacology 28: 637-640, 1985b

Howden CW, Reid JL. Omeprazole, a gastric 'proton pump inhibitor': lack of effect on renal handling of electrolytes and urinary acidification. European Journal of Clinical Pharmacology 26: 639-640, 1984

Howden CW, Reid JL. The effect of antacids and metoclopramide on omeprazole absorption and disposition. British Journal of Clinical Pharmacology 25: 779-781, 1988

Jones DB, Howden CW, Burget DW, Kerr GD, Hunt RH. Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with antisecretory drugs. Gut 28: 1120-1127, 1987

Klinkenberg-Knol EC, Festen HPM, Meuwissen SGM. The effects of omeprazole and ranitidine on 24-hour pH in the distal oesophagus of patients with reflux oesophagitis. Alimentary Pharmacology and Therapeutics 2: 221-228, 1988

Klinkenberg-Knol EC, Jansen JBMJ, Festen HPM, Meuwissen SGM, Lamers CBHW. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. Lancet 12: 349-351, 1987

Lamers CBHW, Lind T, Moberg S, Jansen JBMJ, Olbe L. Omeprazole in Zollinger-Ellison syndrome. Effects of a single dose and of long-term treatment in patients resistant to histamine H_2-receptor antagonists. New England Journal of Medicine 310: 758-761, 1984

Lanzon-Miller S, Pounder RE, Hamilton MR, Ball S, Chronos NAF, et al. Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Alimentary Pharmcology and Therapeutics 1: 239-251, 1987

Lind T, Andersson T, Skanberg I, Olbe L. Biliary excretion of [^{14}]-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

Lloyd-Davies KA, Rutgersson K, Solvell L. Omeprazole in the treatment of Zollinger-Ellison syndrome: a 4-year international study. Alimentary Pharmacology and Therapeutics 2: 13-32, 1988

MacGilchrist AJ, Howden CW, Kenyon CJ, Beastall GH, Reid JL. The effects of omeprazole on endocrine function in man. European Journal of Clinical Pharmacology 32: 423-425, 1987

McKee RF, MacGilchrist AJ, Garden OJ, Forrest JAH, Carter DC. The anti-secretory effect and pharmacokinetics of omeprazole in chronic liver disease. Alimentary Pharmacology and Therapeutics 2: 429-437, 1988

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

Naesdal J, Bankel M, Bodemar G, Gotthard R, Lundquist G, et al. The effect of 20mg omeprazole daily on serum gastrin, 24-h intragastric acidity and bile acid concentration in duodenal ulcer patients. Scandinavian Journal of Gastroenterology 22: 5-12, 1987

Oberg K, Lindström H. Reduction of gastric hypersecretion in Zollinger-Ellison syndrome with omeprazole. Lancet 1: 66-67, 1983

Paulsen O, Hoglund 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

Prichard PJ, Walt RP, Kitchingman GK, Somerville KW, Langman MJS. Oral phenytoin pharmacokinetics during omeprazole therapy. British Journal of Clinical Pharmacology 24: 543-545, 1987

Prichard PJ, Yeomans ND, Mihaly GW, Jones DB, Buckle PJ, et al. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology 88: 64-69, 1985

Regårdh C-G. Pharmacokinetics and metabolism of omeprazole in man. Scandinavian Journal of Gastroenterology 21 (Suppl. 118): 99-104, 1986

Regårdh C-G, Gabrielsson M, Hoffman K-J, Lofberg I, Skanberg I. Pharmacokinetics and metabolism of omeprazole in animals and man – an overview. Scandinavian Journal of Gastroenterology 20 (Suppl. 108): 79-94, 1985

Rondanelli R, Regazzi M, Cerutti R, Cisternino M, Sivelli R, et al. Pharmacokinetics of omeprazole in patients with liver disease. Abstract. European Journal of Clinical Pharmacology 36 (Suppl.): A56, 1989

Sachs G, Wallmark B. The gastric H^+, K^+–ATPase: the site of action of omeprazole. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 3-11, 1989

Sharma BK, Santana IA, Wood EC, Walt RP, Periera M, et al. Intragastric bacterial activity and nitrosation before, during and after treatment with omeprazole. British Medical Journal 289: 717-719, 1984

Sutfin T, Balmer K, Bostrom H, Eriksson S, Hoglund P, et al. Stereoselective interaction of omeprazole with warfarin in healthy men. Therapeutic Drug Monitoring 11: 176-184, 1989

Thompson JN, Barr JA, Collier N, Spencer J, Bush A, et al. Basal, sham fed and pentagastrin-stimulated gastric acid, pepsin and electrolytes after omeprazole 20mg and 40mg daily. Gut 26: 1018-1024, 1985

Tuynman HARE, Festen HPM, Rohss K, Meuwissen SGM. Lack of effect of antacids on plasma concentrations of omeprazole given as enteric-coated granules. British Journal of Clinical Pharmacology 24: 833-835, 1987

Tytgat GNJ, Lamers CBHW, Hameeteman W, Jansen JMBJ, Wilson JA. Omeprazole in peptic ulcers resistant to histamine H_2-receptor antagonists. Alimentary Pharmacology and Therapeutics 1: 31-38, 1987

Utley RJ, Wright R, Beastall GH, Carter DC. The effect of omeprazole on insulin-induced gastric secretion in man. Scottish Medical Journal 30: 96-100, 1985

Vantrappen G, Rutgeerts L, Schurmans P, Coergrachts J-L. Omeprazole (40mg) is superior to ranitidine in short-term treatment of ulcerative reflux esophagitis. Digestive Diseases and Sciences 33: 523-529, 1988

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

Wallmark B. Omeprazole: mode of action and effect on acid secretion in animals. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 12-18, 1989

Walt RP, Gomes MdeFA, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. British Medical Journal 287: 12-14, 1983

Wolfe MM, Soll AH. The physiology of gastric acid secretion. New England Journal of Medicine 319: 1707-1715, 1988

Zeitoun P. Comparison of omeprazole with ranitidine in the treatment of reflux oesophagitis. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 83-87, 1989

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