

Drugs 32: 15-47 (1986)
0012-6667/86/0007-0015/\$16.50/0
© ADIS Press Limited
All rights reserved.

Omeprazole

A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Peptic Ulcer Disease and Zollinger-Ellison Syndrome

Stephen P. Clissold and Deborah M. Campoli-Richards

ADIS Drug Information Services, Auckland

Various sections of the manuscript reviewed by: *W. Beil*, Abteilung Allgemeine Pharmakologie, Medizinische Hochschule Hannover, Hannover, W. Germany; *T. Berglindh*, Center for Ulcer Research and Education, UCLA School of Medicine, Los Angeles, California, USA; *J.D. Gardner*, Department of Health & Human Services, National Institute of Health, Bethesda, Maryland, USA; *C.W. Howden*, Department of Materia Medica, Stobhill General Hospital, Glasgow, Scotland; *M.J.S. Langman*, Department of Therapeutics, University Hospital, Nottingham, England; *W. Londong*, Medizinische Klinik Innenstadt, University of Munich, Munich, West Germany; *D.W. Piper*, Royal North Shore Hospital, St Leonards, New South Wales, Australia; *R.E. Pounder*, Academic Department of Medicine, The Royal Free Hospital, London, England; *G. Sachs*, Center for Ulcer Research and Education, UCLA School of Medicine, Los Angeles, California, USA; *K.-Fr. Sewing*, Abteilung Allgemeine Pharmakologie, Medizinische Hochschule Hannover, Hannover, W. Germany; *B. Simon*, Gastroenterologische Abteilung, Medizinische Universitätsklinik, Heidelberg, W. Germany; *A. Walan*, Department of Internal Medicine, University Hospital, Linköping, Sweden; *R.P. Walt*, Department of Therapeutics, University Hospital, Nottingham, England; *K.G. Wormsley*, Ninewells Hospital, Ninewells, Dundee, Scotland; *N.D. Yeomans*, Department of Medicine, Austin Hospital, Heidelberg, Victoria, Australia.

Contents

Summary	16
1. Pharmacodynamic Studies	19
1.1 Site and Mechanism of Action of Omeprazole	19
1.1.1 Site of Action	20
1.1.2 Mechanism of Action	21
1.2 Effects on Gastric Acid Secretion	23
1.2.1 Animal Studies	23
1.2.2 Studies in Healthy Volunteers	23
1.2.3 Studies in Patients with Duodenal Ulcer Disease	25
1.2.4 Studies in Patients with Zollinger-Ellison Syndrome	26
1.3 Effects on Other Gastric Juice Constituents	26
1.3.1 Pepsin	26
1.3.2 Intrinsic Factor	27
1.4 Effects on Gastrointestinal Hormones	27
1.4.1 Serum Gastrin	27

1.4.2 Other Gastrointestinal Hormones	28
1.5 Effects on Gastric Emptying Rate	28
1.6 Effects on Endocrine Function	28
1.7 Prevention of Experimental Gastric Mucosal Damage	28
1.8 Effects on Gastric Mucosal Morphology	29
1.9 Effects on Intragastric Bacterial Activity and Nitrosamine Concentrations	31
2. Pharmacokinetic Studies	31
2.1 Absorption, Plasma Concentrations, and Bioavailability	31
2.2 Distribution	33
2.3 Metabolism and Excretion	34
2.3.1 Elimination Half-Life	34
2.4 Studies in Patients with Duodenal Ulcer Disease or Zollinger-Ellison Syndrome	35
2.5 Studies in Patients with Chronic Renal Disease	35
2.6 Relationship Between Plasma Concentration and Antisecretory Activity	35
3. Therapeutic Trials	35
3.1 Treatment of Duodenal Ulcers	36
3.1.1 Dose-Ranging Studies	36
3.1.2 Open Studies	36
3.1.3 Omeprazole Compared with Cimetidine or Ranitidine	37
3.2 Treatment of Ulcerative Peptic Oesophagitis	38
3.3 Treatment of Gastric Ulcers	39
3.4 Treatment of Zollinger-Ellison Syndrome	39
4. Side Effects and Effects on Laboratory Variables	40
5. Drug Interactions	41
6. Dosage and Administration	42
7. Place of Omeprazole in Therapy	42

Summary

Synopsis: Omeprazole¹ is a substituted benzimidazole derivative which markedly inhibits basal and stimulated gastric acid secretion. It has a unique mode of action, irreversibly blocking the so-called proton pump of the parietal cell which is supposedly the terminal step in the acid secretory pathway.

In animals, on a weight basis, omeprazole is 2 to 10 times more potent than cimetidine in inhibiting gastric acid secretion. Toxicological studies in rats have shown that very high doses of omeprazole administered for 2 years produce hyperplasia of gastric enterochromaffin-like cells and carcinoids, a few with proliferations into the submucosa. The significance of such findings to the clinical situation is wholly speculative and requires further research. Preliminary studies in patients with duodenal ulcers or Zollinger-Ellison syndrome have found no mucosal changes which would suggest that the drug represents a risk for development of carcinoid tumours at therapeutic dosages.

In patients with duodenal ulcers omeprazole, at dosages of at least 20mg once daily, produced ulcer healing rates of between 60 and 100% after 2 weeks and between 90 and 100% after 4 weeks, even in patients resistant to treatment with H₂-receptor antagonists. Comparative trials clearly demonstrated that omeprazole 20 to 40mg administered once daily was significantly more effective than usual dosage regimens of cimetidine and ranitidine in healing duodenal ulcers during 2 to 4 weeks of treatment. At present no data are available evaluating omeprazole as maintenance therapy once ulcers have healed. Other clinical trials have also shown that omeprazole is effective for treating gastric ulcers, ulcerative peptic oesophagitis, and Zollinger-Ellison syndrome. In patients with Zollinger-Ellison syndrome the profound and long lasting antisecretory activity of omeprazole may make it the drug of choice for treating the massive acid hypersecretion associated with the disease, especially when H₂-receptor antagonists are ineffective. During clinical trials

1 'Losec', 'Lozec', 'Losek' (AB Hässle, Astra; not yet commercially available).

reported to date omeprazole has been very well tolerated but further clinical experience is essential to fully evaluate its safety profile.

Thus, omeprazole represents a pharmacologically unique antisecretory drug which is very effective for rapidly healing peptic ulcers and peptic oesophagitis, and for reducing gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. If the apparent absence of undesirable mucosal morphological changes during treatment with usual doses in patients with peptic ulcer disease is confirmed, it may be a major advance in the treatment of these diseases.

Pharmacodynamic Studies: *In vitro* and *in vivo* animal studies demonstrated that omeprazole produces long lasting inhibition of gastric acid secretion which is likely due to non-competitive binding of a proton-activated derivative to parietal cell (H^+/K^+)-ATPase. Such a mechanism, at the terminal stage of the acid secreting process, means a reduction of intragastric acidity can now be achieved independent of the nature of the primary stimulus. Comparative studies in animals found omeprazole to be some 2 to 10 times more potent than cimetidine on a weight basis.

Single-dose studies in man (healthy volunteers and patients with duodenal ulcer disease or Zollinger-Ellison syndrome) have shown that omeprazole inhibits both basal and stimulated gastric acid secretion in a dose-dependent manner. Following repeat once daily administration, omeprazole has an increasing effect on acid secretion which appears to stabilise after about 3 days. Short term studies indicate that 20 to 30mg once daily is the optimum dosage regimen in healthy volunteers and patients with duodenal ulcer disease in remission; this virtually abolishes gastric acidity within 6 hours and reduces stimulated acid output after 24 hours by 60 to 70%.

In addition to its effects on gastric acidity, omeprazole reduces the total volume of gastric juice secreted and inhibits pepsin output. However, these changes are not as consistent or as great as the effect on acid secretion. Omeprazole 0.35 mg/kg administered intravenously did not significantly affect basal or stimulated intrinsic factor secretion. Furthermore, omeprazole does not seem to have any significant influence on gastric emptying rate, or on the majority of gastrointestinal hormones – apart from gastrin. Short periods of treatment with omeprazole administered once daily usually resulted in elevated serum gastrin levels. Such hypergastrinaemia occurs secondary to a pronounced reduction of intragastric acidity, and returns to normal levels within 1 to 2 weeks of stopping treatment.

Orally, but not parenterally, administered omeprazole seems to be cytoprotective in some animal models of peptic ulcer disease such as Shay ulcers, stress-induced ulcers, and ulcers induced by various necrotising agents. The mechanisms involved are not fully understood but appear to be independent of the established antisecretory properties of omeprazole.

Toxicological studies in rats have demonstrated that supramaximal doses of omeprazole administered for long periods cause gastric enterochromaffin-like cell hyperplasia and carcinoids, a few with proliferations into the submucosa. It has been suggested that hypergastrinaemia, induced by the profound inhibition of gastric secretion causes these changes; their relevance to the therapeutic use of omeprazole remains speculative and further studies are required.

Pharmacokinetic Studies: The absorption characteristics of omeprazole are both formulation- and dose-dependent. Following administration of the drug as a buffered oral solution, buffered encapsulated uncoated granules, or as capsules of enteric-coated granules, mean peak plasma omeprazole concentrations were attained after 20 minutes, 30 minutes, and between 2 and 5 hours, respectively. Interestingly, increased doses of omeprazole produced disproportionately larger increases in mean peak plasma concentration and systemic availability. Similarly, repeat once daily administration for 5 to 7 days resulted in significant elevations of mean peak plasma concentration and area under the plasma concentration-time curve. Since omeprazole is acid labile, these findings could

possibly indicate that the antisecretagogue improves its own absorption and relative bio-availability by inhibiting acid secretion. An alternative explanation involves saturation of enzymes responsible for the first-pass metabolism of omeprazole.

Following intravenous administration omeprazole plasma concentrations decline biexponentially. The apparent volume of distribution of omeprazole is about 0.3 to 0.4 L/kg which is compatible with localisation of the drug in extracellular water. Penetration of omeprazole into red blood cells is low, whereas its plasma protein binding is high – between 95 and 96% in human plasma.

Omeprazole is eliminated rapidly and almost completely by metabolism; no unchanged drug has been recovered in the urine. Following absorption, 3 metabolites of omeprazole have been identified: a sulphone derivative, a sulphide derivative and hydroxyomeprazole. Peak plasma concentrations of the sulphone metabolite are attained shortly after those of unchanged omeprazole, 0.4 to 1.7 hours after peak omeprazole concentrations following administration of capsules of enteric-coated granules. However, unidentified metabolites of omeprazole had a very similar plasma concentration-time curve as the parent drug – in terms of peak concentration and the time to achieve it. Following administration of ^{14}C -omeprazole approximately 60% of total radioactivity is recovered in the urine within 6 hours. Over a 4-day period about 80% of the administered dose was recovered in the urine and the remainder in the faeces. Total plasma clearance is relatively high (32 to 40 L/h) and most studies have reported a mean elimination half-life of omeprazole in healthy subjects of between 0.5 and 1.5 hours (usually about 1 hour).

There are limited data available concerning the pharmacokinetic properties of omeprazole in patients with peptic ulcer disease or Zollinger-Ellison syndrome.

The pharmacokinetic profile of omeprazole does not seem to be altered in patients with chronic renal failure and is not influenced by haemodialysis.

Omeprazole plasma concentration does not correlate with its antisecretory activity at a given time-point; indeed, the drug markedly inhibits acid secretion long after plasma concentrations have decreased below detection limits. However, there does seem to be a significant correlation between antisecretory activity and area under the plasma concentration-time curve.

Therapeutic Trials: Clinical trials have demonstrated that omeprazole at dosages of at least 20mg once daily produces a duodenal ulcer healing rate of between 60 and 100% within 2 weeks and between 90 and 100% within 4 weeks. Dose-finding studies showed that an optimal dosage of omeprazole is between 20 and 40mg once daily. Open clinical studies have confirmed these very high rates of duodenal ulcer healing even in a small group of patients who were refractory to treatment with H_2 -receptor antagonists (alone or in combination with other antiulcer drugs). Appropriately designed comparative clinical trials clearly demonstrated that once-daily administration of omeprazole 20 to 40mg produces significantly more rapid healing of duodenal ulcers after 2 to 4 weeks of treatment than the H_2 -receptor antagonists cimetidine and ranitidine. Additionally, omeprazole 20mg and 40mg once daily elicited significantly greater symptom relief than ranitidine 150mg twice daily, whereas in 2 other studies 30mg and 20mg of omeprazole were indistinguishable from cimetidine 1000 mg/day and ranitidine 300 mg/day, respectively, in this respect. Other clinical studies have shown that omeprazole administered once daily may be effective for treating gastric ulcers and ulcerative peptic oesophagitis. Indeed, omeprazole 40mg once daily was significantly superior to ranitidine 150mg twice daily in 178 patients with reflux oesophagitis. Furthermore, in a double-blind multicentre trial in 184 outpatients with gastric ulceration, omeprazole 20mg once daily was as effective as ranitidine 150mg twice daily and healed 95% of gastric ulcers within 8 weeks.

In patients with Zollinger-Ellison syndrome, omeprazole is a highly potent and long acting antisecretagogue which many authors consider will become the drug of choice for controlling the massive acid hypersecretion associated with the disease. For patients with Zollinger-Ellison syndrome who are resistant to H_2 -receptor antagonists, omeprazole of-

fers a valuable therapeutic alternative to surgery (partial or total gastrectomy) with its inherent risks.

Side Effects: Preliminary experience with omeprazole has found the antisecretagogue to be well-tolerated, producing no consistent side effects or changes in laboratory variables. Wider clinical usage with careful surveillance is needed to fully evaluate the side effect profile of omeprazole.

Dosage and Administration: The usual oral adult dosage of omeprazole seems to be 20mg once daily before breakfast for 2 to 4 weeks for duodenal ulcers and 4 to 8 weeks for gastric ulcers. In patients with Zollinger-Ellison syndrome omeprazole dosage should be individualised so that the smallest dose is administered which reduces gastric acid secretion to less than 10 mEq for the last hour before the next dose. At present, insufficient data are available for dosage recommendations in children.

1. Pharmacodynamic Studies

Omeprazole (fig. 1) is a substituted benzimidazole which markedly inhibits basal and stimulated gastric acid secretion in animals and man. It is the first of a new class of antiulcer drugs likely to be introduced into clinical practice (it is not yet commercially available) and is thought to reduce acid secretion by inhibiting hydrogen/potassium adenosine triphosphatase [(H^+/K^+) -ATPase], believed to be the proton pump of the parietal cell. This mechanism, at the terminal stage of the acid secreting process, means that for the first time intragastric acidity can be reduced independent of the nature of the primary stimulus. Since inhibition of gastric acid is a most important indicator of the therapeutic potential of drugs used to treat peptic

ulceration, omeprazole might be expected to offer some advantages for the treatment of this disease. Independent of its clinical future, omeprazole is already an important pharmacological 'tool' for investigating physiological and biochemical changes that occur in the gastric mucosa and for evaluating the mechanisms of action of gastric acid inhibitors.

1.1 Site and Mechanism of Action of Omeprazole

Superficially, upper gastrointestinal ulceration has a relatively simple underlying aetiology which involves some loss of ability of the mucosa to protect against gastric acid and/or excessive secretion of acid. The complex morphological changes that occur with regard to mucosal cytoprotection in relation to the various conditions found in the upper gut are currently poorly understood and drug treatment has been largely devoted to controlling luminal acidity (Berglindh & Sachs 1985).

Hydrochloric acid, one major cause of upper gastrointestinal tract ulcers, is secreted from parietal (oxyntic) cells by the gastric proton pump [gastric (H^+/K^+) -ATPase], distal to cyclic adenosine monophosphate (cAMP), in response to at least 3 different types of stimulation – cholinergic (vagal), histaminergic and gastrinergic (Sachs 1984) [fig. 2]. It follows that an individual antagonist to any one of the 3 (or more) receptor types will only

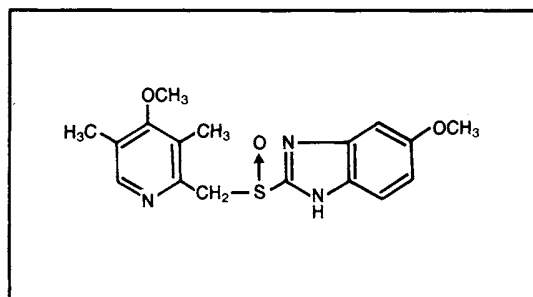


Fig. 1. Structural formula of omeprazole.

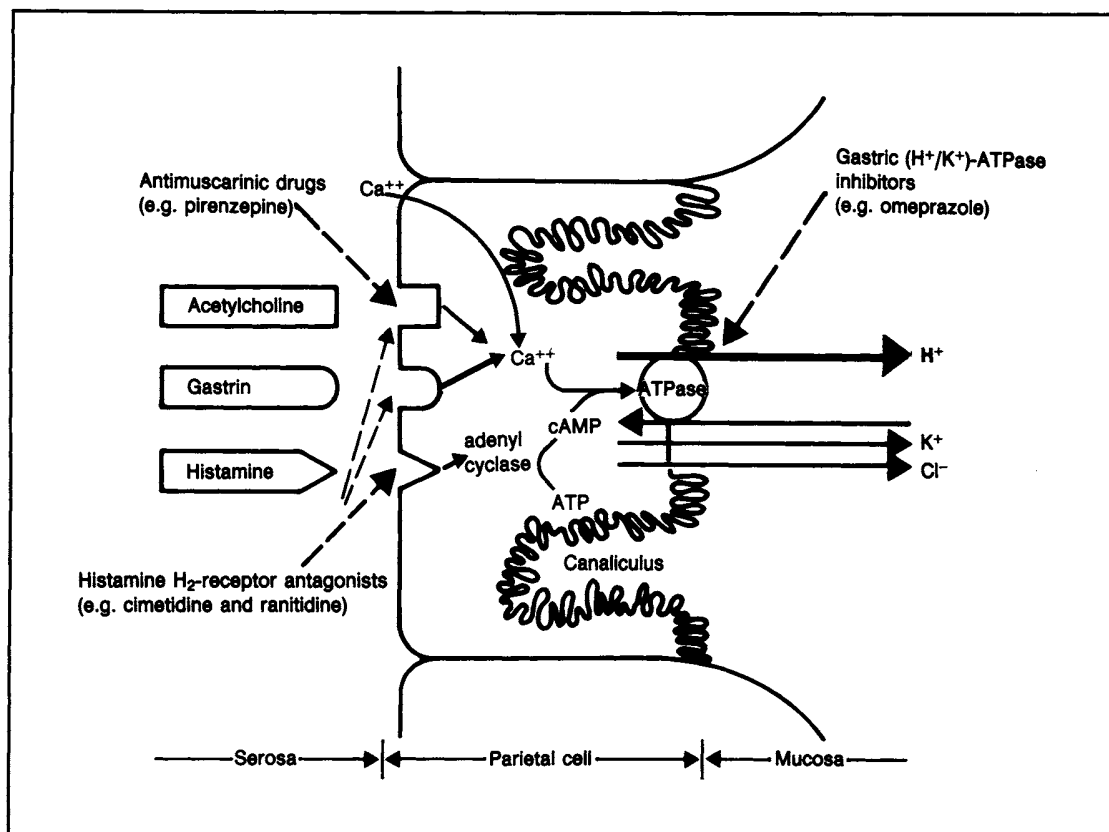


Fig. 2. A simple conceptual model of the parietal cell and some speculated mechanisms involved in the control and inhibition of gastric acid secretion (after Fiasse et al. 1984; Fimmel & Blum 1984; Lewin 1984; Rabon et al. 1983). — — — — — represents proposed mechanisms by which certain classes of antilcer drugs antagonise gastric acid stimulation. — — — — — indicates other additional effects of the H_2 -receptor antagonists (although it is not necessarily at the receptor level) which may contribute to their antisecretory activity (for a review see Bowman & Rand 1980).

partially block gastric acid secretion although there is evidence that the histamine-stimulated system may be dominant since histamine H_2 -receptor antagonists (cimetidine and ranitidine) seem capable of inhibiting a major portion of gastric acid secretion. However, inhibition of the gastric proton pump, probably the terminal stage of the acid secreting pathway from the parietal cell, provides a means of blocking gastric acid secretion by a greater amount. This is the proposed site and mechanism of action of omeprazole (Berglinth & Sachs 1985; Helander et al. 1985; Larsson et al. 1985b) [fig. 2].

1.1.1 Site of Action

Parietal cells are buried deep within the gastric mucosa (slightly beneath peptic cells). Their secretory surfaces are covered with microvilli and are deeply invaginated to form channels termed canaliculi. The gastric proton pump [(H^+/K^+) -ATPase], which has been discovered in frog (Ganser & Forte 1973), hog (Saccomani et al. 1975) and human (Saccomani et al. 1979) gastric mucosa, has been isolated mostly from parietal cells although there is some evidence that it may be present in jejunal (White 1985) and colonic (Gustin & Goodman 1981) mucosa. In gastric mucosa the proton

pump is situated in the apical membrane and tubulovesicles bordering the secretory canaliculi of the parietal cell (for reviews see Berglindh & Sachs 1985; Olbe et al. 1979). Consequently, each canaliculus can be viewed as an invaginated extracellular compartment of low pH (about pH 1). Such an environment should readily accumulate weak bases with a pK_a higher than the pH of the gastric compartment (Berglindh & Sachs 1985; Sachs 1984).

Omeprazole is a substituted benzimidazole and a weak base ($pK_a = 3.97$), which fulfills the criteria for accumulation within the acid space (Brändström et al. 1985). Animal studies have provided strong evidence that the main site of action of omeprazole is indeed in the distal (to cAMP) portion of the parietal cell. Thus, radiolabelled omeprazole administered intravenously to mice was shown to accumulate rapidly in gastric mucosa, liver, kidney, and in the choroid plexus, but after 16 hours high levels of radioactivity remained only in the gastric mucosa. Autoradiography revealed that it was localised in the parietal cells and subsequent electron microscopic autoradiography demonstrated that the radioactive label was almost exclusively found at the secretory surfaces and their immediate vicinity, and in regions of cytoplasm containing the tubulovesicles (Helander et al. 1983, 1985).

Fryklund et al. (1984) using separated and enriched parietal and chief cell fractions from rabbit gastric mucosa showed that omeprazole had a specific inhibitory effect on acid secretion from parietal cells and did not influence stimulated release of pepsinogen from chief cells. However, Défize et al. (1985) found that omeprazole 0.1 mmol/L strongly stimulated secretion of preformed and recently synthesised pepsinogen in isolated rabbit gastric glands even though it decreased pepsinogen synthesis. Similarly, Fimmel et al. (1984) observed that omeprazole 0.1 mmol/L stimulated pepsin release in the *in vitro* perfused mouse stomach model; the mechanism remains uncertain although the increase does not seem to be due to a nonspecific leakage through disruption of chief cell membranes (Défize et al. 1985).

The above findings and those from additional *in vitro* experiments (see section 1.1.2) clearly indicate that the main site of action of omeprazole is in the parietal cell at a point distal to cAMP. It seems likely that the drug binds with (H^+/K^+) -ATPase in the cytoplasm/tubulovesicles and secretory surfaces bordering the canaliculi. However, Keeling et al. (1985) and Beil and Hackbarth (1985) demonstrated that omeprazole also inhibits (Na^+/K^+) -ATPase isolated from dog kidneys, but to a lesser extent than its effects on (H^+/K^+) -ATPase. The authors noted that the acidic compartments of the parietal cell would impart a high degree of selectivity onto omeprazole. Further evidence for the specificity of action of omeprazole is provided by Howden and Reid (1984) who reported that the drug had no demonstrable effects on renal electrolyte or renal acid excretion in healthy volunteers.

1.1.2 Mechanism of Action

Various *in vitro* preparations ranging from isolated gastric mucosa to purified (H^+/K^+) -ATPase from parietal cells have been utilised to help define the mechanism of action of omeprazole (Wallmark et al. 1983, 1985). As can be seen in table I, omeprazole inhibits both basal and stimulated acid secretion (irrespective of whether acid formation was stimulated by histamine, cAMP, high K^+ levels, or exogenously added ATP). In contrast, cimetidine only antagonised histamine-stimulated gastric acid secretion which is consistent with its H_2 -receptor blocking properties. Omeprazole and thiocyanate shared many common pharmacodynamic actions, although only omeprazole directly inhibited isolated (H^+/K^+) -ATPase and withstood attempted reversal by antipyrine of its acid inhibitory properties in isolated gastric mucosa. These findings highlight the late stage in the acid secreting process at which omeprazole exerts its inhibitory effects.

The potency of omeprazole is markedly enhanced in an acidic environment (Beil & Hackbarth 1985; Beil & Sewing 1985; Beil et al. 1985; Im et al. 1985b,c; Keeling et al. 1985; Wallmark et al. 1983, 1984, 1985, 1986). This could be due to a change in parietal cell (H^+/K^+) -ATPase making it more susceptible to the effects of omeprazole at

Table I. Summary of *in vitro* studies designed to elucidate the mechanism of action of omeprazole, compared with cimetidine and thiocyanate as reference drugs, with regard to inhibition of gastric acid secretion (after Beil & Sewing 1984; Larsson & Ryberg 1983; Larsson et al. 1984; Sewing et al. 1983; Wallmark et al. 1983, 1985)

Preparation	Gastric acid stimulant	Inhibitor of gastric acid secretion		
		omeprazole	cimetidine	thiocyanate
Guinea-pig isolated gastric mucosa	Basal	+	—	+
	Histamine	+	+	+
	Dibutyl-yl-cAMP	+	—	—
Rabbit isolated intact gastric glands	Basal	+	—	+
	Histamine	+	+	+
	Dibutyl-yl-cAMP	+	—	+
	K ⁺	+	—	+
Rabbit isolated permeable gastric glands	ATP, K ⁺	+	—	+
Rabbit isolated parietal cells	Histamine	+	+	—
	Dibutyl-yl-cAMP	+	—	—
Pig isolated gastric (H ⁺ /K ⁺)-ATPase	ATP, K ⁺	+	—	—
Guinea-pig (H ⁺ /K ⁺)-ATPase purified from parietal cells	K ⁺	+	—	—
Guinea-pig isolated and enriched parietal cells	Histamine	+	—	—
	Dibutyl-yl-cAMP	+	—	—

Abbreviations: cAMP = cyclic adenosine monophosphate; ATP = adenosine triphosphate; + = drug produced inhibition of gastric acid secretion; — = drug did not produce any inhibition of gastric acid secretion.

low pH. However, at present, the weight of evidence suggests that omeprazole is activated at acidic pH (probably by protonation) and that the H⁺-activated derivative reacts with sulphydryl groups associated with gastric (H⁺/K⁺)-ATPase (Im et al. 1985b,c; Keeling et al. 1985; Sewing & Hanne-mann 1985; Wallmark et al. 1984). Beil and Sewing found that omeprazole could inhibit various sulphydryl-containing ATPases but it was most effective against gastric (H⁺/K⁺)-ATPase. Thus, the unique low pH of the tubulovesicles should make the actions of omeprazole very specific since omeprazole preferentially accumulates at these low pH sites and an acid pH is necessary to activate the drug.

A number of research groups have performed more detailed studies to determine the structure of the active form of omeprazole and the nature of its reaction with gastric (H⁺/K⁺)-ATPase (Im et al.

1985c; Lorentzon et al. 1985; Rackur et al. 1985; Wallmark et al. 1986). Wallmark et al. (1986) recently suggested that omeprazole acts *in vivo*, after being converted in the acid compartments of the parietal cell into a sulphenamide derivative, by forming a disulphide complex with the enzyme (H⁺/K⁺)-ATPase. Alternatively, a sulphenic acid form of omeprazole may react directly with the enzyme. These proposed mechanisms differ from those previously suggested by Im et al. (1985c) and Rackur et al. (1985) and further studies are needed to elucidate the precise mechanisms involved in the inactivation of gastric (H⁺/K⁺)-ATPase.

There is some conflict regarding the nature of the omeprazole/(H⁺/K⁺)-ATPase interaction. *In vitro* studies have shown that the inhibitory effects of omeprazole can be washed out (Berglindh et al. 1985; Sewing et al. 1983, 1985) or they can be reversed by sulphydryl-reducing compounds such as

β -mercaptoethanol. *In vivo* experiments demonstrated that omeprazole produces long lasting inhibition of acid secretion which is likely due to irreversible inhibition of parietal cell (H^+/K^+)-ATPase (Berglindh et al. 1985; Im et al. 1985a). The discrepancy between *in vitro* and *in vivo* results needs to be explained, although there is evidence that omeprazole irreversibly inactivates (H^+/K^+)-ATPase *in vivo* and new enzyme has to be synthesised before gastric acid secretory activity can be restored (Im et al. 1985a).

1.2 Effects on Gastric Acid Secretion

1.2.1 Animal Studies

The effectiveness of omeprazole in inhibiting gastric acid secretion has been investigated in conscious dogs with gastric fistulae or cannulated Heidenhain pouches (Konturek et al. 1984a; Larson & Sullivan 1984; Larsson et al. 1983; Stachura et al. 1983), in an *ex vivo* canine gastric chamber (Larsen et al. 1984), in conscious rats with gastric fistulae (Larsson et al. 1983), and in conscious guinea-pigs with cannulae surgically implanted into the antral portion of the stomach (Batzri et al. 1984). In all of these studies omeprazole, whether administered orally, intravenously, intraduodenally, or subcutaneously, dose-dependently inhibited basal and stimulated (histamine, pentagastrin, bethanechol) gastric acid secretion. Omeprazole was found to be between 2 and 10 times more potent than the H_2 -antagonist, cimetidine, depending upon the route of administration and the experimental model employed (for a review see Larsson et al. 1985b).

The potency of omeprazole following oral administration was generally less than its potency when given intravenously or intraduodenally. This is thought to be due to its instability at low pH resulting in reduced systemic availability (Larsson et al. 1985b). Somewhat surprisingly, considering its short plasma elimination half-life (see section 2.3.1) omeprazole had a very long duration of activity in both dogs and rats (Larson & Sullivan 1984; Larsson et al. 1985b). This accords with the proposed mechanism of action of omeprazole (section 1.1.2) which suggests that the drug irreversibly

binds with (H^+/K^+)-ATPase in the parietal cell. As a consequence of its long duration of action, repeated once daily administration of omeprazole resulted in increased antisecretory activity which reached steady-state after 5 days in the dog (Larsson et al. 1985b).

Thus, animal studies have clearly demonstrated that omeprazole is a potent inhibitor of gastric acid secretion and, reflecting its mode of action, it was equally active against various forms of gastric acid stimulation.

1.2.2 Studies in Healthy Volunteers

Single-Dose Studies

Omeprazole produced a dose-dependent inhibition of basal and stimulated (insulin, peptone, or pentagastrin) gastric acid secretion following oral administration of 20 to 90mg doses to healthy subjects (fig. 3). Since omeprazole degrades rapidly in water solution at low pH (Pilbrant & Cederberg 1985), various formulations have been developed to produce acceptable bioavailability following oral

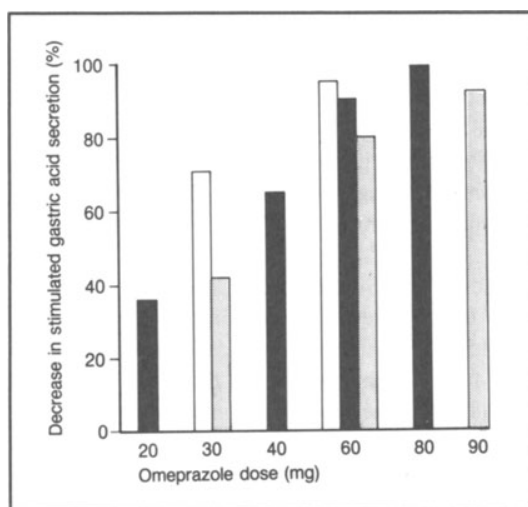


Fig. 3. Mean maximal percentage decrease in pentagastrin (□, ■) or peptone (▨) stimulated gastric acid secretion in groups of healthy volunteers administered oral omeprazole 20 to 90mg as single doses (after □ Howden et al. 1984a; ■ Lind et al. 1983; ▨ Londong et al. 1983).

administration. In single-dose studies omeprazole has been administered as an alkaline (sodium bicarbonate) suspension (Lind et al. 1983; Utley et al. 1985b), as uncoated granules in capsules containing sodium bicarbonate (Londong et al. 1983) or as capsules of enteric-coated granules (Howden et al. 1984a).

Omeprazole was found to have a long duration of action (the degree of acid inhibition remaining unchanged for at least 4 hours) which was significantly correlated to the area under the plasma concentration-time curve (Lind et al. 1983; Londong et al. 1983). Indeed, Lind et al. (1983) showed that higher doses of omeprazole produced significant inhibition of gastric acid secretion for 3 to 4 days (e.g. omeprazole 40mg inhibited acid output by 34 and 18% after 3 and 4 days, respectively). Furthermore, Howden et al. (1984a) reported that omeprazole reduced the volume of gastric juice secreted but not by the same order of magnitude as its effect on acid output. The authors suggest that these observations are further evidence of omeprazole's highly specific site and mode of action.

Intravenously administered omeprazole (infusion of 0.35 mg/kg over 5 minutes) also inhibited both basal and pentagastrin-stimulated gastric acid secretion in healthy volunteers; maximal inhibition occurred after about 90 minutes (Kittang et al. 1985). Maximal inhibition of pentagastrin-stimulated gastric acid secretion was noted after about 2 hours following intraduodenal administration of omeprazole 40 to 80mg (Wilson et al. 1984).

Short Term Studies

In the first repeat-dose clinical study omeprazole 15mg oral suspension was administered once daily to 6 healthy volunteers for 5 days (Lind et al. 1983). The secretory response to pentagastrin-stimulation was determined 2 hours after administration on days 1, 3, and 5, and maximal acid secretion was reduced 48, 74, and 81%, respectively, compared with placebo (fig. 4). On days 3 and 5, 24 hours after the previous day's dose, omeprazole inhibited maximally stimulated acid secretion by 30 to 40%. Thus, as demonstrated in animal studies (see section 1.2.1) repeated once daily

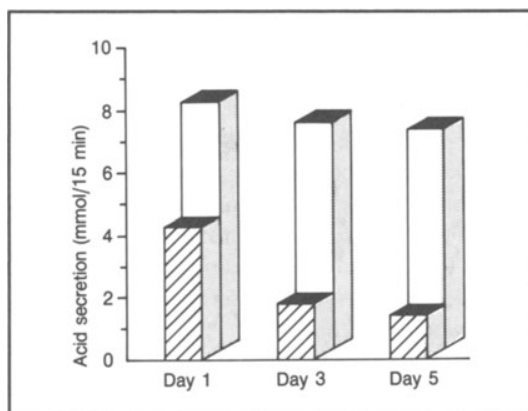


Fig. 4. Maximal acid response to pentagastrin (91 μ g/h intravenously) stimulation in 6 healthy subjects treated once daily with oral omeprazole 15mg (▨) or placebo (□) for 5 days. Measurements were made 2 hours after administration on days 1, 3 and 5 (after Lind et al. 1983).

administration of omeprazole results in an increasing inhibitory action on gastric acid secretion, stabilising after about 3 days (Lind et al. 1983; Müller et al. 1985).

Further studies in which oral omeprazole (usually enteric-coated granules) 5 to 60mg once daily was administered for periods of between 5 and 28 days have generally confirmed the findings of Lind et al. (1983); for a review see Cederberg et al. (1985) [table II]. Overall, the results from these studies indicate that the optimal once daily dosage of omeprazole is 20 to 30mg for reduction of acid secretion; producing almost complete inhibition of maximally stimulated gastric acid secretion within 6 hours (Howden et al. 1984a) and a 60 to 70% reduction of stimulated acid secretion after 24 hours (Cederberg et al. 1984; Müller et al. 1984b). In addition, omeprazole 30mg once daily reduced nocturnal acidity by 76% (Sharma et al. 1983) while 40mg once daily reduced 24-hour median hydrogen ion activity by almost 100% (Prichard et al. 1985b).

Other studies in healthy volunteers have reported that omeprazole 30 or 60mg once daily for 7 to 9 days reduced overnight acid secretion by

Table II. Summary of studies evaluating the effects of repeated dose administration of oral omeprazole in healthy volunteers

References	No. of subjects	Omeprazole dosage (mg once daily) and duration of treatment	Results and comments
Cederberg et al. (1984)	6	EC. 5, 10, 20, 30 and 40mg for 5 days each	PAO measured 24 hours after last dose was reduced 2 to 67% Optimal omeprazole dosage seems to be between 20 and 30mg once daily
Howden et al. (1984a)	12	EC. 30mg for 7 days	Maximal ^a reductions of BAO and PAO were 99.8% and 98.4%, respectively
		EC. 60mg for 7 days	Maximal ^a reductions of BAO and PAO were 99.1% and 99.0%, respectively
Müller et al. (1984a)	8	EC. 30mg for 9 days	BAO measured 24 hours after last dose was reduced ≈ 50% after 5 and 10 days' treatment PAO measured 24 hours after last dose was reduced ≈ 60% after 5 and 10 days' treatment
		EC. 30mg for 9 days	24-hour intragastric acidity was reduced to ≈ 72% and ≈ 82% after 9 days' treatment with 30mg and 60mg omeprazole once daily, respectively
		EC. 60mg for 9 days	
Müller et al. (1984b)	8	EC. 30mg for 28 days	PAO measured 24 hours after last dose was reduced 72% and 10 days later they had returned to pretreatment values
Prichard et al. (1985b)	8	EC. 40mg at 9am or 9pm for 5 days	After 5 days' treatment 24-hour median pH had risen to 5.0 (am) and 4.5 (pm) from 1.9 (pretreatment). This corresponds to > 99% reduction in 24-hour median H ⁺ activity, with am dosage having a greater effect
Sharma et al. (1983)	10	EC. 30mg for 14 days	76% reduction in nocturnal acidity after 14 days. Between days 12 and 29 after treatment there was some evidence of rebound hyperacidity (≈ + 30%)
Sharma et al. (1984a)	16	EC. 40mg for 14 days	PAO measured 24 hours after the last dose was decreased 68%. There was no evidence of rebound hyperacidity 8 to 22 days after treatment

a Measured 6 to 7 hours after administration – the time of expected maximal acid inhibition.

Abbreviations: EC = enteric coated; PAO = peak acid output; BAO = basal acid output; ≈ = approximately.

about 50 and 70%, respectively (Dammann et al. 1983; Wilson et al. 1984).

1.2.3 Studies in Patients with Duodenal Ulcer Disease

Single-dose and short term studies in patients with duodenal ulcer disease, symptomatic or in remission, have confirmed that omeprazole administered orally (20 to 80mg), intragastrically (2 to 6 μmol/kg), or intravenously (120 to 160 mg/day in 2 or 3 divided doses) is a potent inhibitor of in-

tragastric acidity (Hetzel & Shearman 1984; Konturek et al. 1984b; Naesdal et al. 1984; Thompson et al. 1985; Walt et al. 1983, 1984). Single oral doses of omeprazole produced a dose-dependent reduction of mean gastric acid secretion (Hetzel & Shearman 1984) [table III], while short term treatment (1 week) with 30 to 80mg once daily virtually abolished intragastric acidity (Naesdal et al. 1984; Walt et al. 1983). Thompson et al. (1985) administered omeprazole 20 or 40mg once daily for 4 weeks to 9 patients with symptomatic duodenal

Table III. Summary of a double-blind clinical trial in which single morning (8am) doses of enteric-coated omeprazole were administered to 7 male patients with endoscopically confirmed duodenal ulcer disease in symptomatic remission (after Hetzel & Shearman 1984)

Parameter	Omeprazole dose (mg)		
	20	40	80
Reduction of mean total overnight acid output	43%	73%	91%
Median gastric pH	1.6	3.1	7.0
No. of patients whose gastric pH achieved 7.0	3/7 (43%)	4/7 (57%)	7/7 (100%)
Proportion of aspirates with a pH > 4.0	35%	49%	78%
Reduction of mean total overnight volume of gastric secretions	8%	29%	31%

ulcer disease. They found that the major cause of reduced acid output after omeprazole administration was a decreased secretion of the primary acid component of the parietal cell.

Omeprazole 80mg administered intravenously rapidly raised gastric pH to > 4.0 in all patients 1 hour after first administration. However, relatively large doses were needed (compared with oral omeprazole) to maintain gastric pH above 4.0 for 24 hours (Walt et al. 1984, 1985). Similarly, Lind et al. (1986) demonstrated that omeprazole administered intravenously 2 or 3 times a day (total daily dose 160 to 200mg) was able to maintain intragastric pH above pH 4 in practically all patients.

Walt et al. (1983) reported that oral omeprazole 30mg once daily, compared with previous experience with cimetidine 1 g/day and ranitidine 300 mg/day in similar groups of patients, produced a more profound inhibition of gastric hydrogen ion activity (95% vs 48% and 69%, respectively). Additionally, omeprazole increased intragastric pH to > 3.0 in more samples of gastric juice than did

cimetidine or ranitidine; 86% vs 12% and 24%, respectively. Although such historical comparisons are far from ideal, these results do give an indication of the antisecretory properties of omeprazole; the relative potencies reported are in line with those obtained from *in vivo* animal studies (section 1.2.1) and from therapeutic trials in patients with peptic ulceration (section 3.1.3).

1.2.4 Studies in Patients with Zollinger-Ellison Syndrome

Lamers and Jansen (1982) evaluated the effect of a single oral dose of omeprazole 80mg on the secretion of gastric acid in 6 patients with Zollinger-Ellison syndrome. All had hypergastrinaemia (serum gastrin 0.44 to 6.5 µg/L), a positive secretin provocation test and gastric acid hypersecretion (basal acid output 13.3 to 90.8 mmol/hour). Mean gastric acid secretion was inhibited by 98 and 83%, 2 and 24 hours after administration of omeprazole, and clinical symptoms associated with the disease were completely abolished for at least 48 hours. Serum gastrin concentrations were not affected by omeprazole 80mg.

1.3 Effects on Other Gastric Juice Constituents

As noted in section 1.2.2 omeprazole reduces the total volume of gastric juice secreted and consequently some studies have evaluated the effects of the antisecretagogue on other constituents of gastric secretion, mainly pepsin.

1.3.1 Pepsin

Omeprazole does not produce such a consistent inhibitory effect on pepsin secretion as it does on gastric acid output in either healthy subjects or patients with duodenal ulcer disease (Howden et al. 1984a; Kittang et al. 1985; Konturek et al. 1984b; Thompson et al. 1985; Wilson et al. 1984). Kittang et al. (1985) found that intravenously administered omeprazole (0.35 mg/kg) inhibited pentagastrin-stimulated pepsin output by 38% in healthy volunteers. Similarly, Konturek et al. (1984b) reported that omeprazole administered intragastrically (2 or

6 $\mu\text{mol/kg}$) inhibited pepsin output which was stimulated by pentagastrin (49 and 78%, respectively), or by modified sham feeding (44 and 69%, respectively), in 8 patients with duodenal ulcer disease in symptomatic remission. Wilson et al. (1984) administered omeprazole 40 and 80mg directly into the duodenum and observed a significant reduction of stimulated pepsin output 2 hours after dosage. However, during the course of a week's treatment with omeprazole 30 or 60mg once daily, only the 60mg dosage regimen produced a reduction in pepsin output from 50 to 39 mg/h.

Contrasting with the above results, Howden et al. (1984a) observed no significant effects of omeprazole on pepsin secretion. During a single-dose study, omeprazole 30 and 60mg apparently increased pentagastrin-stimulated pepsin output but had no effect on basal pepsin output. After 7 days' treatment with omeprazole 30 or 60mg administered once daily the increase in stimulated pepsin output was greatly reduced compared with the increases observed in the single-dose study. The variable effects of omeprazole on pepsin secretion are not clearly understood and may reflect differences in methodology. Overall, omeprazole does not affect pepsin secretion by the same extent to which it inhibits acid secretion and this is consistent with the proposed mechanism and site of action of the drug (Howden et al. 1984a).

1.3.2 Intrinsic Factor

Parietal cells, in addition to their involvement in the control of gastric acidity, are also thought to secrete Castle's intrinsic factor which is necessary for the absorption of vitamin B₁₂ (Bowman & Rand 1980). Inhibitors of gastric acid secretion have been shown to reduce intrinsic factor secretion but no such effect was observed with omeprazole administered as a single intravenous infusion of 0.35 mg/kg (Kittang et al. 1985). Omeprazole did not affect basal or pentagastrin-stimulated intrinsic factor output and this supports the hypothesis that acid and intrinsic factor have separate secretory pathways within the parietal cell. No data are currently available regarding intrinsic factor secretion during longer periods of treatment with omeprazole.

1.4 Effects on Gastrointestinal Hormones

1.4.1 Serum Gastrin

Single-dose studies in man have not demonstrated any clinically significant effects of omeprazole on fasting or stimulated serum gastrin levels. Thus, Konturek et al. (1984b) found that omeprazole 2 to 6 $\mu\text{mol/kg}$ administered intragastrically did not affect serum gastrin or serum pancreatic polypeptide responses to modified sham feeding in 8 patients with duodenal ulcer disease in clinical remission. Similarly, omeprazole 30 to 90mg administered orally to healthy volunteers had no significant effects on mean fasting gastrin concentrations and serum gastrin responses to peptone or insulin stimulation (Londong et al. 1983; Utley et al. 1985b).

In these studies there were small but statistically insignificant increases in mean fasting serum gastrin concentration and in the plasma gastrin response to insulin infusion. In contrast, Allen et al. (1984) observed a small but statistically significant ($p < 0.05$) increase in basal plasma gastrin concentration 6 hours after administering omeprazole 40mg orally to healthy volunteers. However, omeprazole had no significant effect on postprandial plasma gastrin levels.

During short term clinical studies omeprazole 30 or 60mg administered once daily for 7 to 14 days to healthy volunteers or patients with duodenal ulcer disease in symptomatic remission produced a significant elevation of mean fasting and postprandial serum gastrin concentrations (Festen et al. 1984; Howden et al. 1983; Sharma et al. 1983, 1984c). Festen et al. (1984) found that omeprazole 30mg once daily for 14 days increased fasting and meal-stimulated serum gastrin concentrations and fasting serum pepsinogen I concentrations, but after stopping treatment there was a rapid return to pre-treatment levels. As noted by Sharma et al. (1984c) the hypergastrinaemia associated with continued treatment with omeprazole could potentially promote parietal cell hyperplasia with the risk of rebound hyperacidity when treatment is stopped. Further studies are needed to evaluate changes in intragastric pH after discontinuing omeprazole

therapy, although pharmacodynamic and clinical studies to date have provided no evidence for any rebound effects.

Overall, short term treatment with omeprazole results in increased serum gastrin concentrations which probably occur secondary to a pronounced reduction of intragastric acidity (Cederberg et al. 1985; Müller et al. 1985). Serum gastrin concentrations returned to normal within 1 to 2 weeks of stopping omeprazole therapy.

1.4.2 Other Gastrointestinal Hormones

Allen et al. (1984) evaluated the gastrointestinal peptide response to food in 6 healthy volunteers following oral administration of omeprazole 40mg. Basal and postprandial plasma concentrations of 13 gastrointestinal hormones (gastrin, secretin, insulin, pancreatic polypeptide, pancreatic glucagon, vasoactive intestinal polypeptide, enteroglucagon, gastric inhibitory polypeptide, neurotensin, cholecystokinin, motilin, somatostatin, and gastrin-releasing polypeptide) were measured. Apart from an increase in basal plasma gastrin concentration no significant effect was observed on the plasma concentrations of any of the other peptides involved in gastrointestinal regulation.

1.5 Effects on Gastric Emptying Rate

A single oral dose of omeprazole 90mg had no significant effect on solid or liquid gastric emptying rates in 8 patients with duodenal ulcer disease in symptomatic remission (Horowitz et al. 1984). Similarly, omeprazole did not significantly alter histamine-induced gastric emptying rate in guinea-pigs. This contrasted with the results achieved with the histamine H₂-receptor antagonists cimetidine and ranitidine which inhibited both gastric acid secretion and gastric emptying rate in parallel (Batzri et al. 1985). Larsson et al. (1985b) found that a very high oral dose of omeprazole (400 µmol/kg) inhibited gastric emptying in the rat while lower oral and IV doses had no significant effect.

1.6 Effects on Endocrine Function

Because of the variable effects of the histamine H₂-receptor antagonists cimetidine and ranitidine

on endocrine function (for reviews see Brogden et al. 1978, 1982) some studies have assessed endocrine responses during treatment with omeprazole.

Londong et al. (1983) evaluated the effects of omeprazole 30 to 90mg on thyroid hormones since earlier toxicological studies had suggested that very high doses of the antisecretagogue may inhibit the conversion of thyroxine to tri-iodothyronine (for a review see Ekman et al. 1985). In this single-dose study omeprazole did not have any significant effect on the serum concentrations of thyroxine, tri-iodothyronine, thyroxine-binding globulin, or thyroid-stimulating hormone up to 4.5 hours after administration to 8 healthy subjects. Similarly, Müller et al. (1984b) observed no significant change in thyroid hormone concentrations after 28 days of treatment with omeprazole 30mg once daily in 8 healthy volunteers. Additionally, basal plasma concentrations of prolactin, dehydroepiandrosterone, cortisol, testosterone, 17β-oestradiol, parathormone, insulin, C-peptide, and glucagon were not significantly affected by 28 days' treatment with omeprazole.

Howden et al. (1986) reported that omeprazole 60mg daily for 7 days did not significantly alter basal cortisol concentrations in healthy volunteers. However, it did significantly reduce the peak cortisol response to exogenous ACTH stimulation. The clinical significance of this effect, if any, remains to be determined.

1.7 Prevention of Experimental Gastric Mucosal Damage

Omeprazole administered by routes that enable direct contact with the mucosal surface (oral, intragastric, or intraduodenal) produced a dose-related inhibition of the formation of Shay ulcers, stress-induced ulcers, and gastric ulcers induced by a number of necrotising agents such as acetic acid, aspirin, ethanol, hypertonic sodium chloride, indomethacin, mepirizole and prednisolone in rats (Goto et al. 1984; Kollberg et al. 1984; Konturek et al. 1983; Mattsson et al. 1983; Miyake et al. 1985; Schulman et al. 1984; Yamamoto et al. 1984). However, the protection against induced mucosal

damage does not seem to be due to reduced acid secretion since omeprazole given intravenously or intraperitoneally in doses which completely inhibit acid output is not protective (Kollberg et al. 1984; Mattsson et al. 1983). Furthermore, the duration of its protective action (3 hours) is much shorter than its effects on acid secretion (for a detailed review see Larsson et al. 1985b).

In comparative studies the antisecretory and cytoprotective effects of omeprazole were generally equal to, or exceeded, those of cimetidine in a number of models of peptic ulcer disease (Kollberg et al. 1984; Yamamoto et al. 1984) [table IV]. However, Utley et al. (1985a) observed that cimetidine protected the pylorus-ligated rat against mucosal injury induced by topical aspirin or taurocholate while omeprazole failed to exhibit any cytoprotective activity in this model. In another study, repeat administration of omeprazole 200 mg/kg/day for 2 to 4 weeks produced significantly higher rates of ulcer healing (37.8 and 74.7% after 2 and 4 weeks, respectively) than cimetidine 400

to 450 mg/kg/day (15.8 and 35.8% after 2 and 4 weeks, respectively) in rats administered acetic acid to induce gastric damage (Miyake et al. 1985; Yamamoto et al. 1984).

The mechanism of the apparent cytoprotective actions of omeprazole in some animal models of peptic ulcer disease is not fully understood. Some authors have suggested that it is due to the established antisecretory properties of omeprazole (Goto et al. 1984; Yamamoto et al. 1984), although the lack of effect of parenteral formulations of the drug against experimentally induced mucosal necrosis indicate that this is probably not the major mechanism (Mattsson et al. 1983). It is possible that increased secretion of bicarbonate from the gastric mucosa may have a protective action. However, omeprazole 1 to 100 $\mu\text{mol/L}$ was devoid of any effects on basal or carbachol-stimulated alkali secretion in isolated guinea-pig antral mucosa (Mattsson et al. 1984). Another possible mechanism could involve stimulation of endogenous protective prostaglandins. However, Mattsson et al. (1983) demonstrated that pretreatment with indomethacin had little effect on the protective potency of omeprazole against ethanol-induced ulceration, while Kollberg et al. (1984) and Konturek et al. (1983) found that the cytoprotective activity of omeprazole was unrelated to the biosynthesis of mucosal prostaglandins in rats.

In contrast with the above results from animal studies, omeprazole 5 or 10mg once daily did not reduce aspirin-induced gastric mucosal injury in man (Müller et al. 1986). Nevertheless, Bytzer et al. (1984) observed a significant rise in basal and stimulated prostaglandin E_2 secretion and a significant reduction of acid output in duodenal ulcer patients treated with omeprazole 40 mg/day. Obviously, further research is necessary to clearly define how omeprazole protects the gastric mucosa from some forms of necrotic injury.

1.8 Effects on Gastric Mucosal Morphology

Morphological changes in the gastric mucosa of animals during toxicological screening of newly developed powerful antisecretory drugs has generated

Table IV. Summary of the relative effects of omeprazole (ome) and cimetidine (cim) on gastric acid secretion and experimentally induced gastric lesions in rats (after Yamamoto et al. 1984)

Parameter	ED ₅₀ ^a (mg/kg)		Ratio ^b (cim/-ome)
	cim	ome	
Gastric acid output	300	5.2	58/1
Stress-induced erosions	115	8.7	13/1
Shay ulcers	NS ^c	8.7	
Indomethacin-induced erosions	39.9	1.8	22/1
Aspirin-induced erosions	7.2	0.8	9/1
Prednisolone-induced erosions	70	25.4	3/1
Mepirizole-induced ulcers	29	5.4	5/1

a Dose required for 50% inhibition of the various parameters assessed.

b Ratio ED₅₀cim/ED₅₀ome.

c Cimetidine had no significant effect on the formation of Shay ulcers.

major interest in the safety of this class of agent (for reviews see Elder 1985; Langman 1985; Penston & Wormsley 1986; Wormsley 1984b). In particular, loxidine (an unsurmountable H₂-receptor antagonist) and omeprazole have been the subjects of a great deal of speculation following the publication of results from long term toxicity tests (Daly & Pottage 1985a,b; Jack et al. 1985; Lee 1985; Poynter et al. 1985; Wormsley 1985). The findings for omeprazole have been reviewed below and remain a contentious issue among gastroenterologists. Additional research is clearly needed to elucidate: (a) the mechanism of gastric carcinoid induction in rats, and why it does not occur in mice or dogs; and (b) the clinical relevance, if any, of animal data to the human situation.

Toxicological studies in various animal species for periods of up to 2 years have shown that high doses of omeprazole can produce morphological changes in the gastric mucosa (Ekman et al. 1985). In rats treated with omeprazole 40 to 400 µmol/kg/day, oxyntic mucosal cell hyperplasia was observed. One of the oxyntic mucosal cells, the endocrine enterochromaffin-like cell, had formed carcinoid tumours. A few of these carcinoids exhibited proliferation into the submucosa. Hyperplasia of oxyntic mucosal cells also occurred in dogs and mice, although in these species there was only a very small increase in the number of enterochromaffin-like cells (Ekman et al. 1985). The results of short term mutagenicity studies have all been negative.

Blom (1984) found that orally administered omeprazole 40 µmol/kg/day for 130 days caused an approximate 27% increase in mucosal thickness in rats. This effect was mainly due to an increase in the total number of epithelial cells with an associated increase in the total volume of zymogen granules; the proportion of parietal cells per mm³ of mucosa remained unchanged. Similarly, Stöckmann et al. (1984) demonstrated that oral omeprazole 40 µmol/kg twice daily for 60 days produced a 2-fold increase in enterochromaffin-like cells, without affecting the volume density of somatostatin cells, in corpus mucosa of rats. In antral mucosa the volume density of gastrin cells signifi-

cantly increased. In both these studies, the changes described were fully reversible within 8 to 12 weeks of discontinuing treatment with omeprazole. Larsson et al. (1985a, 1986) noted that increased enterochromaffin-like cell density in rat oxyntic mucosa was directly correlated with elevated circulating gastrin levels which, in turn, were dependent upon the degree of gastric acid inhibition produced by high doses of omeprazole or ranitidine. The authors concluded that it is unlikely that omeprazole or ranitidine have any proliferative effects on enterochromaffin-like cells.

What is the clinical significance of these toxicological findings? Current evidence suggests that the hyperplasia of enterochromaffin-like cells is not directly induced by omeprazole but a physiological response to hypergastrinaemia which is caused by profound long term inhibition of gastric acid secretion. However, other explanations have been proposed (for a review see Wormsley 1984b). As noted in section 1.4.1, short term treatment with omeprazole does elevate serum gastrin concentrations in patients with duodenal ulcer disease in clinical remission or in healthy volunteers, but these increases were nowhere near as great as those reported in the animal toxicology studies. Gastric mucosal changes have been observed with other antisecretory drugs, such as corpus mucosal hyperplasia (H₂-receptor antagonists), chief cell atrophy accompanied by eosinophilia of chief cell granules (famotidine), and hyperplasia of endocrine cells with the formation of gastric tumours (loxidine) [for recent reviews see Ekman et al. 1985; Elder 1985; Langman 1985]. Furthermore, cases of diffuse or nodular enterochromaffin-like cell hyperplasia and tumours in the oxyntic area of the stomach have been reported in patients with markedly elevated serum gastrin concentrations (Ekman et al. 1985).

Mucosal biopsy samples have been taken from some patients treated with omeprazole and it was shown that dosages of 40 mg/day for 4 weeks in duodenal ulcer patients (n = 12) or 20 to 120 mg/day for 6 to 21 months in patients with Zollinger-Ellison syndrome (n = 17) did not significantly alter the proportions of parietal or endocrine cells in

the corpus mucosa (Helander 1985). These data suggest that omeprazole does not represent a carcinogenic risk during short periods of treatment in duodenal ulcer patients or during longer periods of treatment in Zollinger-Ellison syndrome.

In conclusion, it appears that gross overdosing of test animals with omeprazole for long periods exaggerates a physiological response related to profound inhibition of gastric acid secretion. Further studies of gastrointestinal morphology are needed to confirm the apparent absence of adverse mucosal changes during treatment with usual doses in man, including the 'higher' doses that may be required in patients with Zollinger-Ellison syndrome.

1.9 Effects on Intra gastric Bacterial Activity and Nitrosamine Concentrations

Sharma et al. (1984b) reported that omeprazole 30mg daily for 2 weeks significantly decreased nocturnal intragastric acidity and produced significant increases in gastric bacterial count, nitrite, and nitrosamine concentrations in 10 healthy volunteers. As noted by these authors, such nitrogen-containing compounds have been implicated as probable carcinogens in a variety of organs and in many animal species. However, the results presented were not conclusive and the increased concentrations observed could simply reflect a reduction of gastric secretion which would be expected with omeprazole (Wormsley 1984a). An evaluation of the total quantities (as opposed to concentration) of bacteria, nitrites and nitrosamines in gastric juice following omeprazole therapy is needed to clarify these findings.

2. Pharmacokinetic Studies

Omeprazole is an ampholyte (pK_a s of 3.97 and 8.8) which is slightly soluble in water but very soluble in alkaline solutions. As noted in section 1.2.1, omeprazole degrades very rapidly in aqueous solutions of low pH and, as a result, various oral formulations of the drug have been developed to try to limit preabsorption degradation and conse-

quently improve systemic bioavailability. Most early studies with omeprazole used suspensions of the drug in a water solution of methylcellulose also containing sodium bicarbonate. To avoid acidic degradation buffers were usually coadministered with the suspension (Pilbrant & Cederberg 1985). More recently an enteric-coated formulation of omeprazole has been introduced which seems to have overcome many of the problems associated with oral administration.

Although much is already known regarding the pharmacokinetic properties of omeprazole, further information is needed to explain the disproportionate increases in absorption and bioavailability with increasing doses, and to delineate its metabolic pathways. At present only limited pharmacokinetic data are available following administration of omeprazole to patients with peptic ulcer disease.

2.1 Absorption, Plasma Concentration and Bioavailability

A summary of studies evaluating the absorption characteristics of various formulations of omeprazole is presented in table V. The mean time to attain maximum plasma concentrations (T_{max}) was highly formulation dependent; less than 20 minutes for solutions of omeprazole, about 30 minutes for uncoated omeprazole granules, and between 2 and 5 hours for enteric-coated granules of the drug. Absorption of the drug from encapsulated enteric-coated granules was somewhat erratic, but the significance of unpredictable plasma pharmacokinetic data for a drug whose pharmacodynamic activity is not directly related to its plasma concentration (see section 2.6) remains speculative. Indeed, Pritchard et al. (1985b) demonstrated that enteric-coated omeprazole produced sustained inhibition of 24-hour gastric acid secretion despite erratic absorption.

Two interesting trends in the studies summarised in table V are the disproportionately large elevations of the maximal plasma concentration (C_{max}) of omeprazole with increasing dosage (Londong et al. 1983; Regårdh et al. 1985) and the significant increases in C_{max} and area under the

Table V. Summary of pharmacokinetic studies in healthy volunteers evaluating the absorption characteristics of different oral formulations of omeprazole

Omeprazole dose (mg)	Single or repeat dosage	C _{max} (mg/L)	T _{max} (h)	AUC (mg/L · h)
<i>Encapsulated enteric-coated granules (after Howden et al. 1984b; Prichard et al. 1985b)</i>				
40 am	Single dose	0.64	3.0	1.19 ^a
40 am	After 5 daily doses	0.94	2.9	2.22 ^a
40 pm	Single dose	0.30	4.8	0.84 ^a
40 pm	After 5 daily doses	0.71	3.3	2.30 ^a
30	Single dose	0.56	2.3 ^b	1.12 ^c
30	After 7 daily doses	0.71	2.5 ^b	2.02 ^c
60	Single dose	1.67	2.9 ^b	3.05 ^c
60	After 7 daily doses	2.07	3.1 ^b	5.98 ^c
<i>Encapsulated uncoated granules (after Londong et al. 1983)</i>				
30	Single dose	0.52 ^d	≈ 0.5	0.55 ^e
60	Single dose	1.38 ^d	≈ 0.5	1.73 ^e
90	Single dose	2.14 ^d	≈ 0.5	3.45 ^e
<i>Solution of omeprazole coadministered with sodium bicarbonate (after Regårdh et al. 1985)</i>				
20	Single dose	0.66 ^d	0.23	
10	Single dose	0.14 ^d	≈ 0.20 ^d	
40	Single dose	0.86 ^d	≈ 0.27 ^d	
90	Single dose	2.42 ^d	≈ 0.27 ^d	

a AUC to either the last detectable plasma concentration or 12 hours.

b Wide variation in individual times taken to achieve C_{max}.

c AUC 0 to 8 hours.

d Estimated from graphical presentation.

e AUC, time unqualified.

Abbreviations: C_{max} = maximum plasma concentration of omeprazole; T_{max} = time to achieve C_{max}; AUC = area under the plasma concentration-time curve.

plasma concentration-time curve (AUC) after repeated once daily administration for 5 to 7 days (Howden et al. 1984b; Prichard et al. 1985b). Both of these findings could possibly be explained by the gastric acid inhibitory properties of omeprazole. Thus, omeprazole, a highly acid-labile compound, may increase its own relative bioavailability by virtue of its antisecretory activity which reduces the acid degradation of the parent molecule, consequently enhancing the extent of its absorption. Since the drug is rapidly eliminated (see section 2.3.1) and its plasma half-life is not significantly changed with repeat administration (Howden et al.

1984b; Prichard et al. 1985b) it seems likely that any increases in the absorption of omeprazole will be self-limiting and should not result in excessive accumulation. This accords with pharmacodynamic data; repeat once daily administration of omeprazole produced increasing antisecretory effects which reached steady-state after 3 to 5 days (see sections 1.2.1 and 1.2.2). However, a longer term pharmacokinetic study is needed to confirm these speculations.

The plasma concentrations of the sulphone metabolite of omeprazole have also been measured. Mean peak plasma concentrations of omeprazole

sulphone of 0.23 to 0.49 mg/L occurred after 3.4 to 5.6 hours which is a delay of 0.4 to 1.7 hours compared with T_{max} for unchanged omeprazole (Prichard et al. 1985b). Following oral administration of ^{14}C -omeprazole 20mg to healthy volunteers, Regårdh et al. (1985) demonstrated similar findings with respect to omeprazole sulphone. In addition, they observed that unidentified metabolites of omeprazole produced a very similar plasma concentration-time curve (in terms of C_{max} and T_{max}) as the parent drug.

Several studies in healthy volunteers have assessed the bioavailability of various formulations of omeprazole. The bioavailability of unbuffered solutions of omeprazole was 44% of a buffered solution, which indicates that preabsorption acid degradation of unbuffered solutions of omeprazole exceeds 50% (Pilbrant & Cederberg 1985). Regårdh et al. (1985) reported that the mean systemic availability of an oral solution of buffered omeprazole 20mg was 53.6% (range 24.9 to 117.0%) and that bioavailability increased with dosage from 40.3% (10mg) to 58.2% (40mg) and 96.9% (90mg), respectively. The authors suggest that the increase in bioavailability with increased dosage may be due to partial saturation of enzymes responsible for first-pass metabolism. However, as mentioned earlier, omeprazole may improve its own bioavailability by decreasing gastric acid secretion and enhancing the extent of its absorption.

Initial studies with the enteric-coated formulation of omeprazole indicate approximately 65% systemic availability relative to a buffered oral solution (Pilbrant & Cederberg 1985). These authors found that food delayed the absorption of omeprazole and concluded that the drug should be given on an empty stomach. When the enteric-coated granules were administered before a morning meal the length of time between dosage and eating was of no importance. Concomitant administration of a liquid antacid (aluminium magnesium hydroxide/carbonate suspension) had no influence on the bioavailability of omeprazole.

2.2 Distribution

Following intravenous administration of omeprazole 10mg to 8 healthy volunteers plasma ome-

prazole concentrations declined biexponentially and produced an excellent fit to the equation for a 2-compartment model (Regårdh et al. 1985). The mean half-life of omeprazole in the rapidly declining distribution phase ($t_{1/2\alpha}$) was 3.0 (range 2.1 to 4.3) minutes. The mean volume initially available for the distribution of omeprazole was 0.08 L/kg while the apparent volume of distribution at pseudo-distribution equilibrium was 0.31 L/kg. These data indicate that omeprazole undergoes limited tissue distribution and are compatible with localisation of a major fraction of the drug in extracellular water (Regårdh et al. 1985). In a follow-up study omeprazole 10 and 40mg was administered intravenously to groups of 10 healthy volunteers; the volume of the central compartment was calculated to be 0.14 and 0.15 L/kg, respectively, while the apparent volume of distribution was 0.34 and 0.37 L/kg, respectively (Regårdh et al. 1985).

Autoradiographic studies in animals have confirmed the rapid distribution of omeprazole (Heller et al. 1985; Regårdh et al. 1985). In rats, high levels of radioactivity were found in the liver, kidneys, duodenum, stomach and thyroid gland, while in mice radioactivity rapidly reached high levels in the choroid plexus, liver, kidneys, gallbladder, stomach, bladder, and hair follicles. After 4 hours, in the murine model, radioactivity was high only in the gastric mucosa, gastric and mucosal contents, liver and gallbladder. In both species, only small quantities of omeprazole were observed in brain tissue which suggests that the drug and/or its metabolites can only penetrate the blood-brain barrier to a limited extent. However, radioactivity was demonstrated in the fetuses of pregnant mice, indicating that the placental barrier was permeable to omeprazole or its metabolites.

At concentrations covering the normal therapeutic range (0.19 to 19.4 $\mu\text{mol/L}$) omeprazole protein binding was calculated to be between 95 and 96% in human plasma using an ultrafiltration technique (Regårdh et al. 1985). Additional experiments indicated that the drug is primarily bound to serum albumin and α_1 -acid glycoprotein. The penetration of omeprazole into red blood cells is low as estimated by the ratio between the concen-

tration of drug in whole blood and plasma, which was about 0.6 (Regårdh et al. 1985).

2.3 Metabolism and Excretion

Omeprazole is eliminated rapidly and almost completely by metabolism. Following administration of ^{14}C -omeprazole (20mg orally and 10mg intravenously) to 8 healthy volunteers, approximately 60% of total radioactivity was recovered in the urine in the first 6 hours. Additionally, over a 4-day period, about 75 to 78% of the administered dose was recovered in the urine while approximately 18 to 19% was recovered in the faeces (Regårdh et al. 1985). In this study mean total plasma omeprazole clearance was 31.8 (range 3.5 to 49.7) L/h which corresponds to a mean total body (blood) clearance of 52.8 L/h (since the ratio between the blood and plasma concentrations of omeprazole is about 0.6). Comparably high plasma clearance values of 39.5 and 38.0 L/h were reported following intravenous administration of omeprazole 10mg and 40mg, respectively, to groups of 10 healthy subjects (Regårdh et al. 1985).

After absorption, omeprazole is rapidly metabolised and 3 metabolites have been identified in human plasma; omeprazole sulphone, omeprazole sulphide and hydroxyomeprazole (Lagerström & Persson 1984; Mihaly et al. 1983; Prichard et al. 1985b). As noted in section 2.1, peak plasma omeprazole sulphone concentrations are attained shortly after peak omeprazole concentrations (Prichard et al. 1985b; Regårdh et al. 1985). In these studies no omeprazole sulphide was detectable in the plasma. Regårdh et al. (1985) found that during the first 2 hours the plasma level of unidentified metabolites peaked at approximately the same time as unchanged omeprazole and had a similar plasma concentration-time curve as the parent drug, following oral administration of omeprazole 20mg. Unchanged omeprazole has not been recovered in the urine and only a small fraction of an administered dose has been recovered in the urine as the sulphone metabolite (Prichard et al. 1985b; Regårdh et al. 1985). These data indicate that omeprazole sulphone either undergoes further metabolism be-

fore being renally excreted or it is eliminated in the faeces – by biliary secretion or by secretion through the gastrointestinal wall.

Animal studies have shown that omeprazole is oxidised to a sulphone and reduced to a sulphide in the liver (Webster et al. 1984a, 1985). Using isolated perfused rat liver, the production and elimination of omeprazole sulphone were both inhibited by hypoxia while the formation of omeprazole sulphide was enhanced. These results highlight the dependence on oxygen status of the metabolic pathways involved in the hepatic degradation of omeprazole.

Recent studies in dogs, rats and mice have shown that omeprazole is extensively metabolised in these species, and at least 10 metabolites have been identified (Hoffmann 1986; Hoffmann et al. 1986). However, further research is necessary to fully delineate the pathways involved in the metabolic degradation of omeprazole in man, and to determine if the metabolites have any antisecretory activity.

2.3.1 Elimination Half-Life

Most studies in healthy volunteers have demonstrated that omeprazole is rapidly eliminated from plasma with a terminal half-life of between 0.5 and 1.5 hours (Lind et al. 1983; Londong et al. 1983; Prichard et al. 1985b; Regårdh et al. 1985). Howden et al. (1984b), employing a monoexponential pharmacokinetic model, reported elimination half-lives of between 1.73 and 3.30 hours after single or repeated doses of omeprazole 30 or 60mg. However, the erratic absorption of the drug from its enteric-coated formulation (time to achieve maximum plasma concentration ranged from 0.5 to 7.0 hours) and the short duration of the study (8 hours) may have combined to produce an artificially low elimination rate constant and, consequently, an overestimate of plasma elimination half-life.

Following oral administration of enteric-coated omeprazole 40mg the elimination half-lives of the sulphone metabolite of omeprazole were calculated to be 0.64 and 1.64 hours, respectively, for 2 healthy volunteers.

2.4 Studies in Patients with Duodenal Ulcer Disease or Zollinger-Ellison Syndrome

Following oral administration of enteric-coated omeprazole 10 to 60mg there were considerable variations in peak plasma concentrations and the time to achieve them (Sharma et al. 1984c). This erratic absorption of omeprazole in duodenal ulcer patients is similar to that observed in healthy subjects (see section 2.1). In these patients there was a non-linear relationship between dose of omeprazole and AUC and this was highlighted by a near 4-fold increase in AUC when the dose was doubled from 30 to 60 mg/day. It is therefore important that in 3 patients studied mean AUC did not significantly change between the seventh and fourteenth once daily doses of omeprazole (3.6 to 3.3 $\mu\text{mol/L} \cdot \text{h}$), since this shows that drug accumulation did not occur.

A wide variation in the absorption of omeprazole has also been noted in 6 patients with Zollinger-Ellison syndrome after administration of 80mg of an enteric-coated formulation (Lamers et al. 1985). A significant increase in the extent of absorption was observed when omeprazole was given with sodium bicarbonate.

2.5 Studies in Patients with Chronic Renal Disease

Howden et al. (1984c, 1985) evaluated the antisecretory effects and pharmacokinetic characteristics of single 30mg oral doses of omeprazole in 6 patients with chronic renal failure receiving regular haemodialysis. Omeprazole significantly reduced basal and peak acid output in these patients and the antisecretory effects were not influenced by dialysis. Peak plasma omeprazole concentrations of 0.15 to 1.19 mg/L were attained within 0.5 to 2.0 hours and showed marked intersubject variability. Similarly, the AUCs were variable and ranged from 0.14 to 3.25 mg/L \cdot h on day 2 (non-dialysis day) and from 0.10 to 2.37 mg/L \cdot h on day 3 (a dialysis day). There was no difference in the concentration of omeprazole in arterial and venous plasma samples during dialysis and the drug was not detectable

in dialysis fluid. These data indicate that the pharmacokinetic profile of omeprazole is not influenced by haemodialysis.

Recently, Naesdal et al. (1985a) evaluated the pharmacokinetics of ^{14}C -omeprazole after a single intravenous dose of 20mg and a single oral dose of 40mg in 12 patients with chronic renal insufficiency. The derived pharmacokinetic values for unchanged omeprazole were within the range reported for healthy volunteers. Systemic availability was 68%, mean elimination half-life 0.5 hours, and no unchanged drug was detectable in urine. However, the cumulative 24-hour excretion of radioactive metabolites was significantly related to creatinine clearance.

2.6 Relationship Between Plasma Concentration and Antisecretory Activity

Although omeprazole dose-dependently inhibits gastric acid secretion (see section 1.2) its antisecretory activity does not correlate with peak plasma concentrations in animals or man (for reviews see Cederberg et al. 1985; Larsson et al. 1985b; Skånberg et al. 1985). Indeed, animal studies have shown that omeprazole markedly inhibits acid secretion long after plasma levels have decreased below detection limits (Larsson et al. 1985b). Importantly, most studies in animals and man which have assessed plasma concentrations of omeprazole in relation to inhibition of acid secretion have shown a significant correlation between antisecretory activity and AUC. These findings suggest that it is the distribution of the drug to the tissues – and the weight of evidence from pharmacodynamic studies (see section 1.1) indicate that it is to parietal cells in the stomach mucosa in particular – which has a major impact on the antisecretory activity of omeprazole. At present there is no convenient method for estimating the levels of 'active' omeprazole at its site of action and plasma concentration does not appear to be a suitable alternative.

3. Therapeutic Trials

The therapeutic efficacy of oral omeprazole in the treatment of duodenal ulcers has been assessed

in dose-ranging studies, open clinical trials, and a small number of comparisons with the histamine H₂-receptor antagonists cimetidine and ranitidine. The comparative studies were appropriately controlled in comparable groups of patients (with respect to age, sex ratio, number and size of duodenal ulcers, etc.), and included sufficient numbers of patients to identify some statistically significant advantages for omeprazole. No placebo-controlled clinical trials in patients with duodenal ulcers have been published to date. Omeprazole has not been evaluated as maintenance treatment for preventing the recurrence of duodenal ulcers after they have healed.

Other preliminary clinical trials include controlled comparisons of omeprazole and ranitidine in patients with endoscopically confirmed gastric ulcer and in patients with reflux oesophagitis, a placebo-controlled trial in patients with peptic oesophagitis and open therapeutic trials in patients with Zollinger-Ellison syndrome.

3.1 Treatment of Duodenal Ulcers

3.1.1 Dose-Ranging Studies

Omeprazole 10 to 60mg once daily for 4 weeks produced rapid healing of duodenal ulcers (especially at doses of 20mg and above), significant inhibition of peak acid output, and marked relief of epigastric pain and concomitant need for antacid relief (table VI). As previously observed by Prichard et al. (1985a), when the rate of ulcer healing after 2 weeks' treatment is correlated with omeprazole dosage (data from various trials) there appears to be a good dose/response relationship (fig. 5). However, as noted by Humphries and Ekenved (1985) and Hüttemann et al. (1986) there does not appear to be any clinically significant benefit in increasing omeprazole dosage to more than 20mg once daily.

Other dose-evaluating therapeutic trials have shown that omeprazole 30mg once daily is superior to omeprazole 10mg once daily for inhibiting gastric acid secretion (Sharma et al. 1984c; Stenderup et al. 1984), that both morning or evening administration of omeprazole 10mg significantly

raises gastric pH (Prichard et al. 1984), and that an 80mg loading dose of omeprazole (followed by 40mg once daily for 4 weeks) did not influence the ulcer healing rate or symptomatic relief compared with the same treatment not preceded by a loading dose (Naesdal et al. 1985b; Walan et al. 1983).

Sharma et al. (1984c) in a large series of studies in 9 patients with endoscopically proven duodenal ulceration showed that omeprazole 10, 20, and 30mg once daily for 1 week produced a 37, 90, and 97% decrease of 24-hour intragastric acidity, respectively. No additional reductions occurred if the dosage was doubled to 60mg once daily or if treatment with the 30mg dose was extended to 2 weeks. The authors also observed that 1 week after discontinuing omeprazole mean 24-hour gastric acidity was still decreased by 26% but was fully recovered when measured 7 weeks later. In this study fasting plasma gastrin concentrations were significantly increased during treatment phases with all doses of omeprazole and probably reflect the profound antisecretory effects of the drug as well as its prolonged duration of activity.

Prichard et al. (1985a) noted, in agreement with previous studies (Elashoff & Grossman 1980; Korman et al. 1983), that duodenal ulcers were more difficult to heal in patients who smoked than in non-smokers. Omeprazole 30mg once daily was significantly more effective than omeprazole 10mg (both administered for 4 weeks) in healing duodenal ulcers in patients classified as smokers [21/21 (100%) vs 12/16 (75%) respectively, $p < 0.05$].

3.1.2 Open Studies

Open studies in patients with endoscopically confirmed symptomatic duodenal ulcers have demonstrated endoscopic evidence of complete healing in about 80% of patients after 2 weeks and in 96 to 98% of patients after 4 weeks of treatment with omeprazole 30 to 40mg once daily (Blanchi et al. 1984; Scandinavian Multicentre Study 1984). These rates of duodenal ulcer healing are similar to those reported in controlled trials (table VII).

After short term (4-week) treatment with omeprazole, discontinuation of active therapy (ant-

Table VI. Summary of studies of 4 weeks duration evaluating the efficacy of various doses of enteric-coated omeprazole in patients with endoscopically confirmed duodenal ulceration

References	No. of patients	Study design	Omeprazole dose (once daily)	Proportion of patients with healed ulcers (%)		Inhibition of peak acid output (%) after 4 weeks	Comments
				after 2 weeks	after 4 weeks		
Cooperative study (1984)	43	r, o, pg	20mg	90		61	All 4 doses were well tolerated and healed a total of 41/43 ulcers; almost all patients were asymptomatic after 4 weeks' treatment and antacid consumption was minimal
			30mg	100		94	
			40mg	90		91	
			60mg	100		81	
Gustavsson et al. (1983)	32	r, db, pg	20mg	63	93		The 60mg dosage produced a significantly faster ulcer healing rate ($p < 0.02$). Both dosages rapidly alleviated pain and the need for antacid relief
			60mg	100	100		
Hüttemann et al. (1986)	115	r, db, pg	20mg	79	97		Both doses were well tolerated and there was no difference between them in terms of healing rates
			30mg	73	93		
Naesdal et al. (1985b)	44	r, db, pg	40mg	95	100		A loading dose of 80mg given on day 1 did not improve the high healing rate produced by the 40mg dosage
			80mg on day 1 and then 40mg	91	100		
Prichard et al. (1985a)	66	r, db, pg	10mg	50	83		The 30mg dosage produced a more rapid healing of ulcers than the 10mg dosage. Both dosages rapidly alleviated dyspeptic symptoms and the need for antacid relief
			30mg	78	94		

Abbreviations: r = randomised; o = open trial; db = double-blind trial; pg = parallel groups of patients.

acids were permitted for occasional minor episodes of pain) resulted in a relapse rate of 31% (11 of 36 patients) within 6 months (Cooperative Study 1984).

Recently, Tytgat et al. (1985) found that omeprazole 40mg once daily for 4 to 8 weeks was highly effective for treating 17 patients with peptic ulcers (10 duodenal, 3 jejunal, and 4 gastric) who were treated unsuccessfully with histamine H_2 -receptor antagonists (with or without pirenzepine, colloidal bismuth subcitrate or sucralfate) for at least 6 months. Omeprazole virtually abolished acid secretion and 100% of ulcers were healed.

3.1.3 Omeprazole Compared with Cimetidine or Ranitidine

Omeprazole 20 to 40mg once daily has been compared with ranitidine 150mg twice daily and cimetidine 1000 mg/day in comparable (with respect to sex ratio, age, mean ulcer size, etc.) groups of patients with endoscopically confirmed duodenal ulceration (table VII). The results of these clinical trials demonstrate that omeprazole produces significantly more rapid healing of duodenal ulcers in 2 to 4 weeks of treatment than the 2 histamine H_2 -receptor antagonists. Furthermore, the reported ulcer healing rates after 4 weeks' therapy

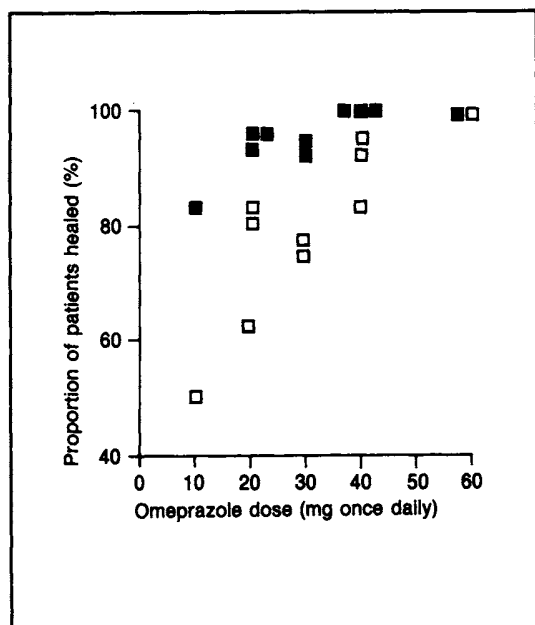


Fig. 5. Percentage of patients with healed duodenal ulcers at various dosages of omeprazole administered once daily for 2 weeks (□) and 4 weeks (■) [after Bardhan et al. 1985; Gustavsson et al. 1983; Hüttemann et al. 1986; Naesdal et al. 1985b; Pritchard et al. 1985a; Walan et al. 1983].

with omeprazole (92 to 100%) compare extremely favourably with those obtained with ranitidine 200 to 320 mg/day (63 to 78%) and cimetidine 800 to 1000 mg/day (45 to 84%), as summarised by Brogden et al. (1982) in a review of controlled therapeutic trials with ranitidine.

Classen et al. (1985a) observed that, independent of whether omeprazole or ranitidine was administered, small ulcers healed more quickly than large ulcers, and smoking delayed healing: ulcers healed during treatment in 87 of 117 (74%) non-smokers and in 113 of 189 (60%) smokers.

Omeprazole 20 or 40mg once daily produced significantly greater symptom relief ($p < 0.05$) than ranitidine 150mg twice daily (Bardhan et al. 1985; Walan et al. 1985). However, no significant difference in pain relief was found between omeprazole 20mg once daily and ranitidine 150mg twice daily (Classen et al. 1985a) or between omeprazole 30mg

once daily and cimetidine 1000 mg/day (Lauritsen et al. 1985).

Lauritsen et al. (1985) followed 91 patients for 6 months after discontinuation of active treatment and found that peptic ulcers recurred in 45% of patients treated with omeprazole and in 59% of those previously treated with cimetidine. Similarly, Walan et al. (1985) followed 79 patients for 6 months and found no significant difference in relapse rate or time to relapse in patients previously successfully treated with omeprazole 20 to 40 mg/day or ranitidine 150mg twice daily.

3.2 Treatment of Ulcerative Peptic Oesophagitis

During a small uncontrolled pilot study, omeprazole 30 mg/day for 8 weeks was found to produce impressive healing of oesophageal ulceration in 7 of 8 patients with peptic oesophagitis (Dent et al. 1984, 1985). Further studies indicated that these changes were due to a profound inhibition of gastric acid secretion, with a concomitant increase in gastric pH, rather than prevention of gastro-oesophageal reflux.

A subsequent 4-week placebo-controlled trial in a larger group of patients with peptic oesophagitis ($n = 63$) demonstrated the significant superiority of omeprazole 20 to 40 mg/day, compared with placebo, in producing endoscopically confirmed healing of oesophagitis (81 vs 6%; $p < 0.001$) and reduction of heartburn (64 vs 14%; $p < 0.001$) [Hetzel et al. 1986]. Dammann et al. (1986) recently reported the results of a multicentre double-blind comparison of omeprazole 40mg once daily and ranitidine 150mg twice daily in 178 patients with reflux oesophagitis. After 3 and 6 weeks of treatment, omeprazole produced significantly higher rates of complete healing or improvement in functional classification (85% and 85%, respectively) than did ranitidine (67% and 45%, respectively). Furthermore, omeprazole more rapidly reduced the symptoms associated with reflux oesophagitis and the difference was statistically significant for heartburn ($p < 0.04$).

Table VII. Summary of randomised double-blind controlled clinical trials comparing omeprazole (O) with ranitidine (R) or cimetidine (C) in patients with endoscopically confirmed duodenal ulcers

References	No. of patients ^a (in each group)	Dosage	Duodenal ulcer healing rate (%)			Comments
			after 2 weeks	after 4 weeks	after 8 weeks	
Bardhan et al. (1985)	104 (34) (36) (34)	O 20mg once daily	83	97	100	Significantly more patients ($p < 0.05$) on both omeprazole 20mg and 40mg were healed at 2 weeks and over the 4-week period compared with ranitidine
		O 40mg once daily	83	100	100	
		R 150mg twice daily	53	82	94	
Classen et al. (1985a)	306 (146) (160)	O 20mg once daily	72	96		Omeprazole was significantly more effective than ranitidine after 2 weeks ($p < 0.02$) but there was no difference between them after 4 weeks
		R 150mg twice daily	59	92		
Lauritsen et al. (1985)	132 (67) (65)	O 30mg once daily	73	92		Omeprazole healed duodenal ulcers significantly more rapidly than cimetidine ($p < 0.01$ after 2 weeks and $p < 0.05$ after 4 weeks)
		C 1000mg daily ^b	46	74		

a Number of patients who completed the study.

b 200mg 3 times daily and 400mg at night.

3.3 Treatment of Gastric Ulcers

Omeprazole 20mg orally each morning was found to be of comparable efficacy to ranitidine 150mg orally twice daily in the treatment of 184 outpatients with endoscopically confirmed gastric ulceration (Classen et al. 1985b). The trial was performed as a multicentre randomised double-blind comparison in 2 comparable (with respect to age, sex, number and size of ulcers, and disease characteristics) groups of patients over a period of 8 weeks. Ulcer healing rates with omeprazole vs ranitidine after 2, 4, and 8 weeks were 43 vs 45%, 81 vs 80%, and 95 vs 90%, respectively. Independent of treatment group, large ulcers and those in the body of the stomach responded most slowly.

3.4 Treatment of Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome, a gastric acid hypersecretory disease caused by benign or malignant gastrin-secreting non-beta islet cell tumours of

the pancreas, is frequently associated with intractable, sometimes fulminating, peptic ulcers (Piper 1982). In the past, treatment has involved partial or total gastrectomy although it is evident that histamine H_2 -receptor antagonists such as cimetidine and ranitidine are effective for the short and long term symptomatic management of the disease (Brogden et al. 1978, 1982). As noted by these authors the H_2 -antagonists are not effective in all patients.

A number of case reports have demonstrated that omeprazole (up to 180 mg/day) can produce rapid and complete inhibition of gastric acid secretion, with marked symptomatic improvement, in patients with Zollinger-Ellison syndrome unresponsive or poorly responsive to drugs such as cimetidine and ranitidine (and their combinations with pirenzepine) [Blanchi et al. 1982; Mignon et al. 1984; Öberg & Lindström 1983; Vezzadini et al. 1984]. Furthermore, Mignon et al. (1984) reported that oral omeprazole adequately controlled acid hypersecretion (with symptomatic relief and ulcer

healing) for periods in excess of 1 year, and the beneficial clinical effects were accompanied by dramatic and sustained reductions in gastric acid secretion as determined by repeated basal output measurements and 24-hour intragastric pH recording. However, repeated ultrastructural studies of the gastric mucosa revealed morphological changes in parietal cells which are not fully understood at the present time and require further study.

In addition to the case reports described above omeprazole has been evaluated in open clinical trials in a small number of patients with Zollinger-Ellison syndrome. Lamers et al. (1984) used once or twice daily omeprazole (30 to 120 mg/day) to treat 7 patients with Zollinger-Ellison syndrome not responsive to histamine H₂-receptor antagonists. Patients were continuously treated for 8 to 19 (mean 14) months; symptoms resolved within 1 to 2 weeks and peptic lesions were healed (assessed endoscopically) after 4 weeks. All patients remained free of symptoms and gastric acid secretion continued to be markedly inhibited by omeprazole. However, 3 patients did require an increase in dosage because 24-hour gastric acid secretion was close to or exceeded 10 mmol/h.

McArthur et al. (1985) evaluated omeprazole (20 to 160 mg/day) in 11 patients with Zollinger-Ellison syndrome which was previously controlled by high doses of histamine H₂-receptor antagonists (alone, or combined with anticholinergic drugs). During long term treatment (1 to 9 months) omeprazole (once daily for 10 patients and twice daily for 1 patient) adequately controlled gastric acid secretion in all patients. After several months' treatment omeprazole was discontinued in 5 patients on maintenance therapy: basal gastric acid secretion was inhibited by > 80% during the first 24 hours after discontinuation and by > 50% during the twenty-fourth to forty-eighth hour (fig. 6). These values highlight the long duration of action of omeprazole.

Lloyd-Davies et al. (1986) presented data from a 4-year international trial in which 80 patients with Zollinger-Ellison syndrome were treated with omeprazole for a mean of 19 months. Each patient was resistant to, or had side effects on, H₂-receptor ant-

agonist therapy. During the course of this trial 13 patients died (not considered drug related), 6 underwent gastrectomy, 4 had successful tumour resection and 4 withdrew for other reasons; the remainder were effectively controlled by omeprazole (> 90% of patients required \leq 120 mg/day; median 60 to 70 mg/day).

4. Side Effects and Effects on Laboratory Variables

Clinical experience with omeprazole is, at present, limited and the drug has only been used for extended periods (> 8 weeks) in small numbers of patients with Zollinger-Ellison syndrome. Most other studies with omeprazole have been of short duration (2 to 8 weeks) and, in the majority of patients with peptic ulcer disease, the drug was well tolerated and produced no consistent side effects or changes in laboratory variables.

In the therapeutic trials reviewed in section 3, omeprazole infrequently caused adverse effects of clinical consequence and, in comparative studies, it was tolerated as well as other antisecretory drugs such as cimetidine and ranitidine. Isolated adverse effects possibly attributable to omeprazole included diarrhoea, nausea, abdominal colic, numbness of the extremities, weakness, dizziness, headache, etc. These effects were generally mild and transient and did not require a reduction of dosage. The only patient withdrawn from therapy complained of severe persistent nausea following 3 weeks' treatment with omeprazole 40mg once daily. At this preliminary stage in its development insufficient data are available to assess accurately the relative incidence of individual adverse effects associated with omeprazole therapy in patients with peptic ulcer disease.

Omeprazole (up to 180 mg/day) has been used to treat patients with Zollinger-Ellison syndrome for up to 19 months (see section 3.2) and, as yet, no serious side effects or significant changes in laboratory variables have been reported.

In one of the first clinical trials with omeprazole in patients with duodenal ulcers, 10 of 32 patients treated with the antisecretagogue (20 or 60 mg/day)

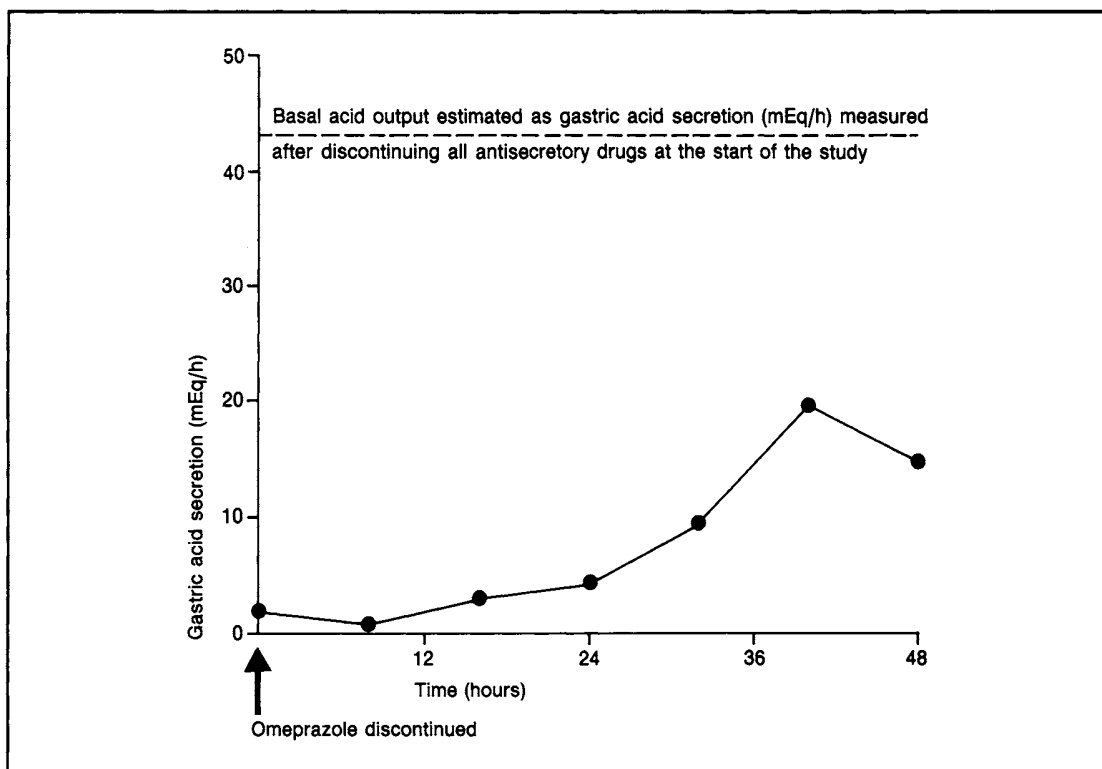


Fig. 6. Change in gastric acid secretion rate after discontinuing omeprazole (mean dose 56mg) in 5 patients treated for Zollinger-Ellison syndrome (after McArthur et al. 1985). For further details see text.

had raised serum alanine aminotransferase concentrations although in most patients the increases were slight and transient (Gustavsson et al. 1983). Since this initial observation no other clinical trials have noted a significant association between omeprazole treatment and indicators of liver dysfunction. Furthermore, the research group who published the original report have since performed a controlled tolerance test in 60 healthy volunteers (Löf et al. 1984). In this study omeprazole 40mg once daily for 2 weeks did not significantly alter serum concentrations of alanine aminotransferase and there was no difference between omeprazole and placebo with regard to liver function tests.

5. Drug Interactions

Cimetidine has been reported to produce some clinically significant drug interactions through in-

hibition of hepatic microsomal mixed function oxidase, whereas ranitidine which does not contain an imidazole ring is less prone to cause important reactions (Henry et al. 1984b). Consequently, a number of investigators have evaluated the potential of omeprazole, a benzimidazole derivative, to interfere with the metabolism of concurrently administered drugs (Gugler & Jensen 1984, 1985; Henry et al. 1984a,b; Webster et al. 1984b,c). Results from studies to date indicate that omeprazole inhibits the oxidative metabolism of some drugs and further research is needed to assess the clinical consequences, if any, of therapeutic doses of omeprazole on the hepatic degradation of concomitantly administered drugs.

An initial study in healthy volunteers reported that omeprazole 40 mg/day for 7 days produced a 130% increase in mean elimination half-life of di-

azepam (from 36.9 to 85.0 hours), with consequent significant increases in plasma diazepam concentrations and significant decreases in total body clearance (Gugler & Jensen 1984). Omeprazole 40 mg/day for 7 days also reduced the plasma clearance of phenytoin from 25.1 to 21.4 ml/kg · hour and increased elimination half-life by 27% (from 20.7 to 26.3 hours; Gugler & Jensen 1985). In another trial in healthy volunteers, omeprazole 60 mg/day for 14 days prolonged the half-life of antipyrine by about 10% and reduced its metabolic clearance by about 14% (Henry et al. 1984b). Aminopyrine $^{14}\text{CO}_2$ half-life in the same subjects was increased by 21% while the proportion of dose which was demethylated was reduced by 19%. In 9 healthy subjects omeprazole 30 mg/day for 14 days had no effect on antipyrine metabolism and produced smaller, statistically insignificant changes in aminopyrine metabolism.

Animal studies have found that omeprazole 40 mg/kg and cimetidine 30 mg/kg produced similar prolongations of phenobarbitone-induced sleeping time (Henry et al. 1984a) and that a 10mg bolus of omeprazole increased the elimination half-life of antipyrine in rat isolated perfused liver by 41%. This latter effect was significantly less than that produced by a 5mg bolus of cimetidine (Webster et al. 1984b,c). Regårdh et al. (1985) showed that omeprazole 20 or 400 $\mu\text{mol/kg}$ administered orally had only a moderate effect on hexobarbital sleeping time and aminopyrine half-life in rats. These results were in contrast to much greater changes produced by cimetidine. *In vitro* studies with human liver microsomes demonstrated that omeprazole is a stronger inhibitor of 7-ethoxycoumarin deethylase activity than cimetidine (Gugler & Jensen 1985).

6. Dosage and Administration

The usual oral adult dose of omeprazole for the treatment of peptic ulcers (oesophageal, gastric, duodenal, jejunal) is 20mg once daily before breakfast. Treatment should be continued until the ulcers are healed; usually 2 to 4 weeks in duodenal ulcers and 4 to 8 weeks in gastric ulcers. Longer durations

of treatment may be needed for patients who smoke and for patients with particularly large peptic ulcers.

Experience with omeprazole in patients with Zollinger-Ellison syndrome is limited, but the indications are that total daily dosages of up to 180mg (on a once or twice daily basis) produce marked inhibition of gastric acid secretion with significant symptomatic improvement. If possible the dosage should be individualised so that the smallest dose of omeprazole is administered which reduces gastric acid secretion to < 10 mEq/h for the last hour before the next dose.

Insufficient data are available at present for dosage recommendations in children.

7. Place of Omeprazole in Therapy

Suppression of gastric acid secretion by histamine H_2 -receptor antagonists such as cimetidine and ranitidine is now a well established means of treating patients with peptic ulcer disease. Nevertheless, these drugs are not always completely successful in healing peptic ulcers. Importantly, a small proportion of patients treated with H_2 -receptor antagonists are resistant to prolonged periods of treatment (Pounder 1984).

Omeprazole is a powerful non-competitive inhibitor of gastric acid secretion which, by virtue of its mechanism of action at the terminal stage of the acid secreting pathway, can virtually abolish gastric acidity if large enough doses are administered. Preliminary clinical studies have clearly shown that once-daily administration of omeprazole heals duodenal ulcers significantly more rapidly than usual dosages of cimetidine and ranitidine. Overall, studies in duodenal ulcer patients have demonstrated that omeprazole at daily doses of 20mg or greater cures more than 90% of patients treated within 2 to 4 weeks. These data suggest that, even at this early stage in its development, omeprazole can be considered a highly effective alternative to currently available treatments for the short term (2 to 8 weeks) management of duodenal ulcers. At present no data are available reporting the use of omeprazole as maintenance therapy once the ulcers have healed.

Preliminary studies in small groups of patients have also demonstrated the effectiveness of omeprazole in patients with gastric ulcers (in whom 20mg once daily was as effective as ranitidine 150mg twice daily), in patients with peptic oesophagitis (in whom 40mg once daily was significantly superior to ranitidine 150mg twice daily), and in patients with duodenal ulcers refractory to treatment with H₂-receptor antagonists (alone or combined with other antisecretory drugs).

Additionally, omeprazole is extremely effective in patients with Zollinger-Ellison syndrome. Most studies have concluded that it is a highly potent and long acting antisecretagogue which promises to become the drug of choice for controlling the massive acid hypersecretion associated with the disease. Since many patients with Zollinger-Ellison syndrome are resistant to conventional drug treatment, omeprazole would seem to offer a valuable medical alternative to surgery (partial or total gastrectomy) with its associated risks.

Thus, omeprazole is pharmacologically unique, and highly effective in inhibiting gastric acid secretion. However, questions concerning its safety have arisen. In the clinical trials reported to date omeprazole has been very well tolerated both in patients and in healthy volunteers. Isolated increases in liver enzymes have been reported but they were usually of a transient nature; with wider clinical experience the clinical significance, if any, of these changes will be established. The most contentious safety findings have been the discovery of enterochromaffin-like cell hyperplasia and carcinoid tumours, with a few cases of proliferations into the submucosa in rats treated with large doses of omeprazole (sufficient to completely abolish gastric acid secretion) for periods of 2 years. Available data are consistent with the theory that these effects are not due to a direct carcinogenic action of omeprazole but are a physiological response to profound gastric acid inhibition and consequent hypergastrinaemia. Similar effects have been observed with other antisecretory drugs and in some patients with diseases associated with high circulatory concentrations of gastrin. Further studies are needed to confirm these speculations and the pre-

liminary reports that omeprazole does not produce mucosal morphological changes at therapeutic doses in patients with peptic ulcer disease. Until such additional evidence is forthcoming, it would seem prudent to avoid long term treatment with high doses of omeprazole (i.e. those likely to completely inhibit acid secretion) except in Zollinger-Ellison syndrome. In the meantime, if long term treatment is considered necessary (such as in patients with Zollinger-Ellison syndrome) then endoscopic surveillance, acid secretory status, and perhaps mucosal biopsies should be checked intermittently.

In summary, initial studies have clearly demonstrated that omeprazole is very effective for rapidly healing peptic ulcers, and for reducing gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. Although the need for additional morphological studies noted above is clearly very important, omeprazole appears to be a major advance in the treatment of peptic ulcer disease, peptic oesophagitis and Zollinger-Ellison syndrome.

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
- Bardhan KD, Bianchi Porro G, Bose K, Hinchliffe RFC, Lazzaroni M, et al. Comparison of two different doses of omeprazole versus ranitidine in duodenal ulcer (DU) healing. *Gut* 26: A557-A558, 1985
- Batzri S, Dubois A, Harmon JW, Moskowitz D. Demonstration of direct influence of histamine H₂-receptors on gastric emptying in guinea pig using histamine antagonists and omeprazole. *Gastroenterology* 88: 1318, 1985
- Batzri S, Weichbrod RH, Harmon JW, Dubois A. Acid secretion in a chronic awake guinea pig model: effects of omeprazole and cimetidine. *Gastroenterology* 86: 1022, 1984
- Beil W, Hackbarth I. Acid activation of omeprazole is important for its selective action on parietal cell K⁺/H⁺-ATPase. *Naunyn - Schmiedeberg's Archives of Pharmacology* 329 (Suppl.): R65, 1985
- Beil W, Mäde S, Hannemann H, Zimmer KO, Sewing K-Fr. Characteristics of K⁺/H⁺-ATPase inhibition by omeprazole and omeprazole sulfide. *Hepato-gastroenterology* 32: 47, 1985
- Beil W, Sewing K-Fr. Inhibition of partially purified K⁺/H⁺-ATPase from guinea-pig isolated and enriched parietal cells by substituted benzimidazoles. *British Journal of Pharmacology* 82: 651-657, 1984
- Beil W, Sewing KF. Acid activation makes omeprazole a specific K⁺/H⁺-ATPase inhibitor. *Gastroenterology* 88: 1320, 1985
- Berglindh T, Hansen D, Bergqvist E. Irreversible inhibition by omeprazole. The in vivo-in vitro connection. *Gastroenterology* 88: 1322, 1985
- Berglindh T, Sachs G. Emerging strategies in ulcer therapy: pumps and receptors. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 7-14, 1985

- 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
- Blanchi A, Rotenberg A, Soule J-C, Delchier J-C, Morin T, et al. Traitement de l'ulcère duodénal en poussée par l'oméprazole. *Gastroentérologie Clinique et Biologique* 8: 943-946, 1984
- Blom H. Effects of long term treatment with omeprazole on the gastric mucosal morphology. *Scandinavian Journal of Gastroenterology* 19 (Suppl. 98): 55, 1984
- Bowman WC, Rand MJ (Eds). *Textbook of Pharmacology*, 2nd ed., Blackwell Scientific Publications, Oxford, 1980
- Brändström A, Lindberg P, Junggren U. Structure activity relationships of substituted benzimidazoles. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 15-22, 1985
- Brogden RN, Carmine AA, Heel RC, Speight TM, Avery GS. Ranitidine. *Drugs* 24: 267-303, 1982
- Brogden RN, Heel RC, Speight TM, Avery GS. Cimetidine. *Drugs* 15: 93-131, 1978
- Bytzer P, Bekker C, Bukhave K, Rask-Madsen J. Gastric prostaglandin E_2 release following acid reduction by cimetidine, omeprazole, and parietal cell vagotomy (PCV) in duodenal ulcer patients. *Acta Medica Scandinavica* (Suppl. 685): 47, 1984
- Cederberg C, Ekenved G, Lind T, Olbe L. Acid inhibitory characteristics of omeprazole in man. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 105-112, 1985
- Cederberg C, Lind T, Axelsson M, Olbe L. Long term acid inhibitory effect of different daily doses of omeprazole 24 hours after dosing. *Gastroenterology* 86: 1043, 1984
- Classen M, Dammann HG, Domschke W, Hengels KJ, Hüttemann W, et al. Kurzzeit-Therapie des Ulcus duodeni mit Omeprazol und Ranitidin. *Deutsche Medizinische Wochenschrift* 110: 210-215, 1985a
- Classen M, Dammann HG, Domschke W, Hüttemann W, Londong W, et al. Abheilungsraten nach Omeprazol- und Ranitidin- Behandlung des Ulcus ventriculi. *Deutsche Medizinische Wochenschrift* 110: 628-633, 1985b
- Cooperative Study. Omeprazole in duodenal ulceration: acid inhibition, symptom relief, endoscopic healing, and recurrence. *British Medical Journal* 289: 525-528, 1984
- Daly MJ, Pottage A. Antisecretory drugs and gastric cancer. *British Medical Journal* 291: 900, 1985a
- Daly MJ, Pottage A. Antisecretory drugs and gastric cancer. *British Medical Journal* 291: 1646-1647, 1985b
- Dammann HG, Blum AL, Lux G, Rehner M, Riechen EO, et al. Unterschiedliche Heilungstendenz der Refluxösophagitis nach Omeprazol und Ranitidin. *Deutsche Medizinische Wochenschrift* 111: 123-128, 1986
- Dammann HG, Müller P, Seitz HK, Simon B. Säuresekretionsverhalten unter einer mehrtägigen Omeprazol-Gabe. *Schweizerische Medizinische Wochenschrift* 113: 895-898, 1983
- Defize J, Pals G, Frants RR, Westerveld BD, Festen HPM, et al. The influence of omeprazole on the synthesis and secretion of pepsinogen in isolated rabbit gastric glands. *Biochemical Pharmacology* 34: 3693-3699, 1985
- Dent J, Downton J, Buckle P, Heddle R, Toouli J, et al. Omeprazole heals peptic esophagitis by elevation of intragastric pH. *Gastroenterology* 88: 1363, 1985
- Dent J, Heddle R, Downton J, Mackinnon J, Toouli J, Lewis I. Omeprazole heals ulcerative peptic esophagitis. *Gastroenterology* 86: 1062, 1984
- Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C. Toxicological studies on omeprazole. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 53-69, 1985
- Elashoff JD, Grossman MI. Smoking and duodenal ulcer. *Gastroenterology* 79: 181, 1980
- Elder JB. Inhibition of acid and gastric carcinoids. *Gut* 26: 1279-1283, 1985
- Festen HPM, Thijs JC, Lamers CBHW, Jansen JMBJ, Pals G, et al. Effect of oral omeprazole on serum gastrin and serum pepsinogen I levels. *Gastroenterology* 85: 1030-1034, 1984
- Fiasse R, Tomé G, Dive Ch. L'Oméprazole, médicament d'avenir pour le traitement du syndrome de Zollinger-Ellison et de l'ulcère duodénal? *Acta Gastro-Enterologica Belgica* 47: 555-568, 1984
- Fimmel CJ, Berger MM, Blum AL. Dissociated response of acid and pepsin secretion to omeprazole in an in vitro perfused mouse stomach. *American Journal of Physiology* 247: G240-G247, 1984
- Fimmel CJ, Blum AL. Substituierte Benzimidazole - eine neue Dimension der Ulkustherapie? *Wiener Klinische Wochenschrift* 4: 149-153, 1984
- Fryklund J, Wallmark B, Larsson H, Helander HF. Effect of omeprazole on gastric secretion in H^+ , K^+ -ATPase and in pepsinogen-rich cell fractions from rabbit gastric mucosa. *Biochemical Pharmacology* 33: 273-280, 1984
- Ganser AL, Forte JG. K^+ -stimulated ATPase in purified microsomes of bullfrog oxyntic cells. *Biochimica et Biophysica Acta* 307: 169-180, 1973
- Goto Y, Olbe L, Walsh JH, Debas HT. Prevention of stress ulceration by omeprazole is due to its antisecretory action. *Gastroenterology* 86: 1094, 1984
- Gugler R, Jensen JC. Omeprazole inhibits elimination of diazepam. *Lancet* 1: 969, 1984
- Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism. *Gastroenterology* 89: 1235-1241, 1985
- Gustavsson S, Adami H-O, Löf L, Nyberg A, Nyrén O. Rapid healing of duodenal ulcers with omeprazole. *Lancet* 2: 124-125, 1983
- Gustin MC, Goodman DBP. Isolation of brush-border membrane from the rabbit descending colon epithelium. Partial characterization of a unique K^+ -activated ATPase. *Journal of Biological Chemistry* 256: 10651-10656, 1981
- Helander HF. Stereological data on parietal and endocrine cells of the gastric corpus in patients treated with omeprazole. *Gastroenterology* 88: 1416, 1985
- Helander H, Ramsay C-H, Regårdh C-G. Localization of omeprazole and metabolites in the mouse. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 95-104, 1985
- Helander HF, Smolka A, Ramsay C-H, Sachs G, Fellenius E. Localization of gastric K^+ , H^+ -ATPase. *Hepato-gastroenterology* 30: 74, 1983
- Henry DA, Gerkens JF, Brent P, Somerville K. Inhibition of drug metabolism by omeprazole. *Lancet* 2: 46-47, 1984a
- Henry DA, Somerville KW, Kitchingman G, Langman MJS. Omeprazole: effects on oxidative drug metabolism. *British Journal of Clinical Pharmacology* 18: 195-200, 1984b
- Hetzel DJ, Dent J, Laurence BH, Reed WD, Narielvala F, et al. Omeprazole heals reflux oesophagitis: a placebo controlled trial. *Gut* 27: A609, 1986
- Hetzel DJ, Shearman DJC. Omeprazole inhibition of nocturnal gastric secretion in patients with duodenal ulcer. *British Journal of Clinical Pharmacology* 18: 587-590, 1984
- Hoffmann K-J. Identification of the main urinary metabolites of omeprazole after an oral dose to rats and dogs. In press, 1986
- Hoffmann K-J, Renberg L, Olovsson S-G. Comparative metabolic disposition of oral doses of omeprazole in the dog, rat, and mouse. In press, 1986
- Horowitz M, Hetzel DJ, Buckle PJ, Chatterton BE, Shearman DJC. The effect of omeprazole on gastric emptying in patients with duodenal ulcer disease. *British Journal of Clinical Pharmacology* 18: 791-794, 1984
- 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, Kenyon CJ, Beasall 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, 1986

- 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 AL, et al. Antisecretory effect and oral pharmacokinetics of omeprazole in patients with chronic renal failure. *European Journal of Clinical Pharmacology* 28: 637-640, 1985
- Howden CW, Payton CD, Meredith PA, Macdougall AI, Reid JL, et al. Influence of haemodialysis on the antisecretory effect and oral pharmacokinetics of omeprazole in chronic renal failure. *Gut* 25: A1182, 1984c
- 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, Forrest JAH. Effect of omeprazole on gastric acid secretion in human volunteers. *Gut* 24: 497, 1983
- Humphries, TJ, Ekenved G. The therapeutic dose response profit for oral omeprazole in the acute therapy of duodenal ulcer: a summary. *American Journal of Gastroenterology* 80: 861, 1985
- Hüttemann W, Rotner HG, duBosque G, Rehner M, Hebbeln H, et al. 20 versus 30mg omeprazole once daily: effect on healing rates in 115 duodenal ulcer patients. *Digestion* 33: 117-120, 1986
- Im WB, Blakeman DP, Davis JP. Irreversible inactivation of rat gastric (H^+K^+)-ATPase *in vivo* by omeprazole. *Biochemical and Biophysical Research Communications* 126: 78-82, 1985a
- Im WB, Blakeman DP, Sachs G. Reversal of antisecretory activity of omeprazole by sulfhydryl compounds in isolated rabbit gastric glands. *Biochimica et Biophysica Acta* 845: 54-59, 1985b
- Im WB, Sih JC, Blakeman DP, McGrath JP. Omeprazole, a specific inhibitor of gastric (H^+K^+)-ATPase, is a H^+ -activated oxidizing agent of sulfhydryl groups. *Journal of Biological Chemistry* 260: 4591-4597, 1985c
- Jack D, Poynter D, Smith RN. Antisecretory drugs and gastric cancer. *British Medical Journal* 291: 675, 1985
- Keeling DJ, Fallowfield C, Milliner KJ, Tingley SK, Ife RJ, et al. Studies on the mechanism of action of omeprazole. *Biochemical Pharmacology* 34: 2967-2973, 1985
- Kittang E, Aadland E, Schjønby H. Effect of omeprazole on the secretion of intrinsic factor, gastric acid and pepsin in man. *Gut* 26: 594-598, 1985
- Kollberg B, Isenberg JI, Johansson C. Cytoprotective effect of omeprazole on the rat gastric mucosa. In Allen et al. (Eds) *Mechanisms of mucosal protection in the upper gastrointestinal tract*, pp. 351-356. Raven Press, New York, 1984
- Konturek SJ, Brzozowski T, Radecki T. Protective action of omeprazole, a benzimidazole derivative, on gastric mucosal damage by aspirin and ethanol in rats. *Digestion* 27: 159-164, 1983
- Konturek SJ, Cieszkowski M, Kwiecién N, Konturek J, Tasler J, et al. Effect of omeprazole, a substituted benzimidazole, on gastrointestinal secretions, serum gastrin, and gastric mucosal blood flow in dogs. *Gastroenterology* 86: 71-77, 1984a
- Konturek SJ, Kwiecién N, Obtutowicz W, Kopp B, Olesky J. Action of omeprazole (a benzimidazole derivative) on secretory responses to sham feeding and pentagastrin and upon serum gastrin and pancreatic polypeptide in duodenal ulcer patients. *Gut* 25: 14-18, 1984b
- Korman MG, Hansky J, Eaves ER, Schmidt GT. Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. *Gastroenterology* 85: 871-874, 1983
- Lagerström P-O, Persson B-A. Determination of omeprazole and metabolites in plasma and urine by liquid chromatography. *Journal of Chromatography* 309: 347-356, 1984
- Lamers CBHW, Jansen JBMJ. Inhibition of gastric acid secretion in Zollinger-Ellison syndrome by omeprazole, a potent and long-acting antisecretory drug. *Gut* 23: A907, 1982
- Lamers CBHW, Lind T, Moberg S, Jansen JBMJ, Olbe L. Omeprazole in Zollinger-Ellison syndrome. *New England Journal of Medicine* 310: 758-761, 1984
- Lamers CBHW, Teunissen L, Jansen JBMJ. Absorption of omeprazole in Zollinger-Ellison syndrome is accelerated by alkali. *Gut* 26: A1134-A1135, 1985
- Langman MJS. Antisecretory drugs and gastric cancer. *British Medical Journal* 290: 1850-1852, 1985
- Larsen KR, Maas VA, Carlsson E. The effects of omeprazole, a proton pump inhibitor, on pentagastrin-stimulated blood flow and oxygen consumption in the ex-vivo canine gastric chamber. *Gastroenterology* 86: 1153, 1984
- Larson GM, Sullivan HW. Omeprazole, a long-lasting inhibitor of gastric secretion. *Journal of Surgical Research* 36: 503-507, 1984
- Larsson H, Carlsson E, Håkansson R, Mattsson H, Sundler F. Relation of plasma gastrin concentrations and oxyntic mucosal ECL density during inhibition of gastric acid secretion in the rat. *Gut* 26: A558, 1985a
- Larsson H, Carlsson E, Junggren U, Olbe L, Sjöstrand SE, et al. Inhibition of gastric acid secretion by omeprazole in the dog and rat. *Gastroenterology* 85: 900-907, 1983
- Larsson H, Carlsson E, Mattsson H, Lundell L, Sundler F, et al. Plasma gastrin and gastric enterochromaffinlike cell activation and proliferation. *Gastroenterology* 90: 391-399, 1986
- Larsson H, Carlsson E, Sundell G. Effects of omeprazole and cimetidine on gastric acid secretion and right atrial beating frequency in isolated organ preparations from the guinea pig. *Digestion* 29: 12-18, 1984
- Larsson H, Mattsson H, Sundell G, Carlsson E. Animal pharmacodynamics of omeprazole. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 23-26, 1985b
- Larsson H, Ryberg B. Omeprazole increases K^+ net flow during stimulated conditions in the mammalian gastric mucosa *in vitro*. *Physiologist* 26: A116, 1983
- Lauritsen K, Rune SJ, Bytzer P, Kelbaek H, Jensen KG, et al. Effect of omeprazole and cimetidine on duodenal ulcer. *New England Journal of Medicine* 312: 958-961, 1985
- Lee FI. Antisecretory drugs and gastric cancer. *British Medical Journal* 291: 1723, 1985
- Lewin MJM. Omeprazole: un nouveau mécanisme d'action et une efficacité sans précédent dans le traitement de l'hypersécrétion acide gastrique. *Gastroentérologie Clinique et Biologique* 8: 939-942, 1984
- 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
- Lind T, Moore M, Olbe L. Intravenous omeprazole: effect on 24-hour intragastric pH in duodenal ulcer patients. In press, 1986
- Lloyd-Davies KA, Rutgersson K, Sölvell L. Omeprazole in Zollinger-Ellison syndrome: four-year international study. Submitted for publication, 1986
- Londong W, Londong V, Cederberg C, Steffen H. Dose-response study of omeprazole on meal-stimulated gastric acid secretion and gastrin release. *Gastroenterology* 85: 1373-1378, 1983
- Löof L, Adami H-O, Gustavsson S, Nyberg A, Nyrén O, Lundborg P. Omeprazole: no evidence for frequent hepatic reactions. *Lancet* 1: 1347-1348, 1984
- Lorentzon P, Eklundh B, Brändström A, Wallmark B. The mechanism for inhibition of gastric ($H^+ + K^+$)-ATPase by omeprazole. *Biochimica et Biophysica Acta* 817: 25-32, 1985
- Mattsson H, Andersson K, Larsson H. Omeprazole provides protection against experimentally induced gastric mucosal lesions. *European Journal of Pharmacology* 91: 111-114, 1983
- Mattsson H, Carlsson K, Carlsson E. Omeprazole is devoid of effect on alkaline secretion in isolated guinea pig antral mucosa. In Allen et al. (Eds) *Mechanisms of mucosal protection in the upper gastrointestinal tract*, pp. 141-146. Raven Press, New York, 1984
- McArthur KE, Collen MJ, Maton PN, Cherner JA, Howard JM,

- et al. Omeprazole: effective, convenient therapy for Zollinger-Ellison syndrome. *Gastroenterology* 88: 939-944, 1985
- Mignon M, Alcabes G, Lehy T, Nguyen Phuoc BK, Vattier J, et al. Modifications sécrétoires, pHmétriques, et ultrastructurales gastriques au cours d'un traitement prolongé par l'oméprazole dans une forme sévère de syndrome de Zollinger-Ellison. *Gastroentérologie Clinique et Biologique* 8: 947-954, 1984
- Mihaly GW, Prichard PJ, Smallwood RA, Yeomans ND, Louis WJ. Simultaneous high-performance liquid chromatographic analysis of omeprazole and its sulphone and sulphide metabolites in human plasma and urine. *Journal of Chromatography* 278: 311-319, 1983
- Miyake H, Fukuda K, Masuda Y, Okabe S. Effects of a proton pump inhibitor, omeprazole, on healing of acetic acid-induced gastric ulcers in rats. *Gastroenterology* 88: 1504, 1985
- Müller P, Dammann HG, Seitz H, Simon B, Kommerell B. Repeated omeprazole administration and human gastric secretion. *Italian Journal of Gastroenterology* 16: 6-8, 1984a
- Müller P, Dammann HG, Simon B. Human acid secretion during and after 18 days' treatment with omeprazole. *Italian Journal of Gastroenterology* 17: 96-97, 1985
- Müller P, Dammann H-G, Simon B. Akute Schädigung der Magenschleimhaut durch Acetylsalicylsäure. *Arzneimittel-Forschung* 36: 265-268, 1986
- Müller P, Seitz HK, Simon B, Dammann HG, Feurle G, et al. Vierwöchige Omeprazol-Gabe: Einfluß auf Säureverhalten und basale Hormonspiegel. *Zeitschrift für Gastroenterologie* 22: 236-240, 1984b
- Naesdal J, Andersson T, Bodemar G, Larsson R, Regårdh CG, et al. Pharmacokinetics of ^{14}C omeprazole in patients with impaired renal function. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 113): 34, 1985a
- Naesdal J, Bodemar G, Walan A. Effect of omeprazole, a substituted benzimidazole, on 24-h intragastric acidity in patients with peptic ulcer disease. *Scandinavian Journal of Gastroenterology* 19: 916-922, 1984
- Naesdal J, Lind T, Bergsäker-Aspöy J, Bernklev T, Farup PG, et al. The rate of healing of duodenal ulcers during omeprazole treatment. *Scandinavian Journal of Gastroenterology* 20: 691-695, 1985b
- Öberg K, Lindström H. Reduction of gastric hypersecretion in Zollinger-Ellison syndrome with omeprazole. *Lancet* 1: 66-67, 1983
- Olbe L, Berglindh T, Elander B, Helander H, Fellenius E, et al. Properties of a new class of gastric acid inhibitors. *Scandinavian Journal of Gastroenterology* 14 (Suppl. 55): 131-135, 1979
- Penston J, Wormsley KG. H_2 -Receptor antagonists and gastric cancer. *Medical Toxicology* 1: 163-168, 1986
- Pilbrant Å, Cederberg C. Development of an oral formulation of omeprazole. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 113-120, 1985
- Piper DW (Ed.). *Peptic ulcer*. ADIS Press, Auckland, 1982
- Pounder RE. Duodenal ulcers that will not heal. *Gut* 25: 697-702, 1984
- Poynter D, Pick CR, Harcourt RA, Selway SAM, Ainge G, et al. Association of long lasting unsurmountable histamine H_2 blockade and gastric carcinoid tumours in the rat. *Gut* 26: 1284-1295, 1985
- Prichard PJ, Rubinstein D, Jones DB, Dudley FJ, Smallwood RA, et al. Double blind comparative study of omeprazole 10mg and 30mg daily for healing duodenal ulcers. *British Medical Journal* 290: 601-603, 1985a
- Prichard PJ, Yeomans ND, Jones DB, Louis WJ, Smallwood RA. Effects of morning or evening dosage with 10mg omeprazole on 24 hour gastric pH in duodenal ulcer patients in remission. *Gut* 25: 1181, 1984
- 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, 1985b
- Rabon E, Cuppoletti J, Malinowska D, Smolka A, Helander HF, et al. Proton secretion by the gastric parietal cell. *Journal of Experimental Biology* 106: 119-133, 1983
- Rackur G, Bickel M, Fehlhaber H-W, Herling A, Hitzel V, et al. 2-[(2-pyridylmethyl)sulfinyl]benzimidazoles: acid sensitive suicide inhibitors of the proton transport system in the parietal cell. *Biochemical and Biophysical Research Communications* 128: 477-484, 1985
- Regårdh C-G, Gabrielsson M, Hoffman K-J, Löfberg I, Skåberg I. Pharmacokinetics and metabolism of omeprazole in animals and man – an overview. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 79-94, 1985
- Saccamani G, Chang HH, Mihas AA, Crago S, Sachs G. An acid transporting enzyme in human gastric mucosa. *Journal of Clinical Investigation* 64: 627-635, 1979
- Saccamani G, Shah G, Spenney G, Sachs G. Characterization of gastric mucosal membranes. VIII. *Journal of Biological Chemistry* 250: 4802-4809, 1975
- Sachs G. Pump blockers and ulcer disease. *New England Journal of Medicine* 310: 785-786, 1984
- Scandinavian Multicentre Study. Gastric acid secretion and duodenal ulcer healing during treatment with omeprazole. *Scandinavian Journal of Gastroenterology* 19: 882-884, 1984
- Schulman N, Bank S, Kranz V. Effects of omeprazole on ethanol and cold-restraint stress induced gastric ulcers. *Gastroenterology* 86: 1239, 1984
- Sewing K-Fr, Harms P, Schulz G, Hannemann H. Effect of substituted benzimidazoles on acid secretion in isolated and enriched guinea pig parietal cells. *Gut* 24: 557-560, 1983
- Sewing KF, Beil W, Hannemann H. The *in vitro* inhibitory effect of omeprazole on parietal cell H^+ -transport is reversible. *Gastroenterology* 88: 1581, 1985
- Sewing K-Fr, Hannemann H. Studies on the mechanism of action of omeprazole. *Naunyn-Schmiedeberg's Archives of Pharmacology* 329 (Suppl.): R65, 1985
- Sharma BK, Lundborg P, Pounder RE, Axelson M, Ohman M, et al. Acid secretory capacity after treatment with omeprazole. *Gastroenterology* 86: 1246, 1984a
- Sharma BK, Santana IA, Walt RP, Pounder RE. Intragastric acidity after treatment with omeprazole. *Gut* 24: A973, 1983
- Sharma BK, Santana IA, Wood EC, Walt RP, Pereira M, et al. Intragastric bacterial activity and nitrosation before, during, and after treatment with omeprazole. *British Medical Journal* 289: 717-719, 1984b
- Sharma BK, Walt RP, Pounder RE, Gomes M De FA, Wood EC, Logan LH. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. *Gut* 25: 957-964, 1984c
- Skånberg I, Carlsson E, Karlsson A, Larsson H, Lofberg I, et al. The pharmacokinetics of omeprazole and correlation to inhibition of gastric acid secretion. *Acta Physiologica Scandinavica* 124 (Suppl. 542): 266, 1985
- Stachura J, Konturek SJ, Cieszkowsky M, Dabrows W, Zakrzewska J, et al. Comparison of the effect of omeprazole – a substituted benzimidazole – and ranitidine – a potent H_2 -receptor antagonist – on histamine-induced gastric acid secretion and the ultrastructure of canine parietal cells. *Hepato-Gastroenterology* 30: 205-210, 1983
- Stenderup J, Mertz A, Wandall JH, Bonnevie O. The inhibition of gastric-acid secretion by omeprazol in daily doses of 10 and 30mg. *Scandinavian Journal of Gastroenterology Suppl.* 98: 48, 1984
- Stöckmann F, Fölsch UR, Bonatz G, Wülfrath M, Creutzfeldt W. Influence of a substituted benzimidazole (omeprazole) on rat gastric endocrine cells. *Digestive Diseases and Sciences* 29 (Suppl.): 835, 1984
- Thompson JN, Barr JA, Collier N, Spencer J, Bush A, et al. Basal, sham feed and pentagastrin stimulated gastric acid, pepsin and

- electrolytes after omeprazole 20mg and 40mg daily. *Gut* 26: 1018-1024, 1985
- Tytgat GNJ, Lamers CBHW, Wilson JA, Hameeteman W, Jansen JBMJ, et al. 100% healing with omeprazole of peptic ulcers resistant to histamine H₂-receptor antagonists. *Gastroenterology* 88: 1620, 1985
- Uttley RJ, Salim ASM, Carter DC. Effect of cimetidine and omeprazole on aspirin- and taurocholate-induced gastric mucosal damage in the rat. *Gut* 26: 770-775, 1985a
- Uttley RJ, Wright R, Beastall GH, Carter DC. The effect of omeprazole on insulin induced gastric secretion in man. *Scottish Medical Journal* 30: 96-100, 1985b
- Vezzadini P, Tomassetti P, Toni R, Bonora G, Labò G. Omeprazole in the medical treatment of Zollinger-Ellison syndrome. *Current Therapeutic Research* 35: 772-776, 1984
- Walan A, Bardhan KD, Bianchi Porro G, Bose K, Hinchliffe RFC, et al. A comparison of two different doses of omeprazole versus ranitidine in duodenal ulcer healing. *Gastroenterology* 88: 1625, 1985
- Walan A, Bergsäker-Aspöy J, Farup P, Gillberg R, Halvorsen L, et al. Four week study of the rate of duodenal ulcer healing with omeprazole. *Gut* 24: A972, 1983
- Wallmark B, Brändström A, Larsson H. Evidence for acid-induced transformation of omeprazole into an active inhibitor of (H⁺ + K⁺)-ATPase within the parietal cell. *Biochimica et Biophysica Acta* 778: 549-558, 1984
- Wallmark B, Carlsson E, Larsson H, Brändström A, Lindberg P. New inhibitors of gastric acid secretion: properties and design of H⁺, K⁺-ATPase blockers. In press, 1986
- Wallmark B, Jaresten B-M, Larsson H, Ryberg B, Brändström A, et al. Differentiation among inhibitory actions of omeprazole, cimetidine, and SCN⁻ on gastric acid secretion. *American Journal of Physiology* 245: 964-971, 1983
- Wallmark B, Lorentzon P, Larsson H. The mechanism of action of omeprazole - a survey of its inhibitory actions *in vitro*. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 37-52, 1985
- Walt RP, Gomes M de FA, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. *British Medical Journal* 287: 12-14, 1983
- Walt RP, Reynolds JR, Langman MJS, Smart HL, Kitchingman G, et al. Intravenous omeprazole rapidly raises intragastric pH. *Gut* 26: 902-906, 1985
- Walt RP, Reynolds JR, Langman MJS, Smart HL, Somerville KW, et al. Intravenous omeprazole rapidly raises intragastric pH. *Gut* 25: A1139, 1984
- Webster LK, Jones DB, Mihaly GW, Morgan DJ, Smallwood RA. Effect of hypoxia on the disposition of omeprazole and two metabolites by isolated perfused rat liver. *Clinical and Experimental Pharmacology and Physiology* (Suppl. 8): 47, 1984a
- Webster LK, Jones DB, Mihaly GW, Morgan DJ, Smallwood RA. Effect of hypoxia on oxidative and reductive pathways of omeprazole metabolism by the isolated perfused rat liver. *Biochemical Pharmacology* 34: 1239-1245, 1985
- Webster LK, Jones DB, Mihaly GW, Smallwood RA. Effect of omeprazole and polyethylene glycol-400 on antipyrine elimination by the isolated perfused rat liver. *Journal of Pharmacy and Pharmacology* 36: 470-472, 1984b
- Webster LK, Jones DB, Smallwood RA. How potent is the inhibition of drug metabolism by omeprazole? *Lancet* 2: 761, 1984c
- White JF. Omeprazole inhibits H⁺ secretion by *Amphiuma jejunum*. *American Journal of Physiology* 248: G256-G259, 1985
- Wilson JA, Boyd EJS, Wormsley KG. Omeprazole inhibits nocturnal and pentagastrin-stimulated gastric secretion in man. *Digestive Diseases and Sciences* 29: 797-801, 1984
- Wormsley KG. Intragastric bacterial activity and nitrosation before, during, and after treatment with omeprazole. *British Medical Journal* 289: 1007, 1984a
- Wormsley KG. Assessing the safety of drugs for the long-term treatment of peptic ulcers. *Gut* 25: 1416-1423, 1984b
- Wormsley KG. Antisecretory drugs and gastric cancer. *British Medical Journal* 291: 1504, 1985
- Yamamoto O, Okada Y, Okabe S. Effects of a proton pump inhibitor, omeprazole, on gastric secretion and gastric and duodenal ulcers or erosions in rats. *Digestive Diseases and Sciences* 29: 394-401, 1984

Authors' address: Stephen P. Clissold, ADIS Drug Information Services, Centorian Drive, Private Bag, Mairangi Bay, Auckland 10 (New Zealand).