

Drugs 42 (1): 138-170, 1991  
 0012-6667/91/0007-0138/\$16.50/0  
 © Adis International Limited. All rights reserved.

DRE1 48

## Omeprazole

### An Updated Review of its Pharmacology and Therapeutic Use in Acid-Related Disorders

*Donna McTavish, Micaela M.-T. Buckley and Rennie C. Heel*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by: **G. Bianchi Porro**, Gastrointestinal Unit, L. Sacco Hospital, Milan, Italy; **K.D. Bardhan**, Rotherham District General Hospital, Rotherham, England; **C.M. Bate**, Department of Gastro-Enterology, Royal Albert Edward Infirmary, Wigan, England; **S. Dahlgren**, Department of Surgery, University of Umeå, Umeå, Sweden; **J. Dent**, Gastroenterology Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia; **A.S. Guerreiro**, Hospital Pulido Valente, Lisbon, Portugal; **C.W. Howden**, Division of Digestive Diseases and Nutrition, University of South Carolina School of Medicine, Columbia, South Carolina, USA; **J.B.M.J. Jansen**, Department of Gastroenterology, University Hospital, Leiden, The Netherlands; **R.T. Jensen**, Cell Biology Section, National Institute of Diabetes, Digestive and Kidney Diseases, Bethesda, Maryland, USA; **T. Lind**, Department of Surgery II, University of Göteborg, Göteborg, Sweden; **I.N. Marks**, Gastro-Intestinal Clinic, Groote Schuur Hospital, Cape Town, South Africa; **P.N. Maton**, Oklahoma Foundation for Digestive Research, Oklahoma City, Oklahoma, USA; **D.W. Piper**, Royal North Shore Hospital, St Leonards, New South Wales, Australia; **R.E. Pounder**, University Department of Medicine, Royal Free Hospital, London, England; **J. Rademaker**, Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; **N. Takeguchi**, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Toyama, Japan.

## Contents

139	Summary
142	1. Overview of Pharmacological Properties
142	1.1 Mechanism of Action
142	1.2 Effects on Gastric Secretion and Plasma Gastrin Levels
143	1.3 Influence on Gastric Mucosal Morphology
144	1.4 Prevention of Experimental Gastric Mucosal Damage
144	1.5 Other Effects
146	1.6 Pharmacokinetic Properties
146	2. Therapeutic Use
147	2.1 Duodenal Ulcers
147	2.1.1 Noncomparative, Dose Finding and Placebo-Controlled Studies
148	2.1.2 Comparisons with Histamine H <sub>2</sub> -Receptor Antagonists
149	2.2 Gastric Ulcers
149	2.2.1 Noncomparative Studies
150	2.2.2 Comparisons with Histamine H <sub>2</sub> -Receptor Antagonists and Other Antiulcer Agents
151	2.3 Treatment of Ulcers Poorly Responsive to Histamine H <sub>2</sub> -Receptor Antagonists
152	2.4 Prevention of Ulcer Recurrence
154	2.5 Reflux Oesophagitis

155	2.5.1 Prevention of Reflux Oesophagitis Recurrence
157	2.6 Zollinger-Ellison Syndrome
159	3. Tolerability
159	3.1 Short Term Tolerability
160	3.2 Long Term Tolerability
161	4. Drug Interactions
161	5. Dosage and Administration
161	6. Place of Omeprazole in Therapy

## **Summary**

### Synopsis

*Omeprazole is the first of a new class of drugs, the acid pump inhibitors, which control gastric acid secretion at the final stage of the acid secretory pathway and thus reduce basal and stimulated acid secretion irrespective of the stimulus.*

*In patients with duodenal or gastric ulcers, omeprazole as a single 20mg daily dose provides more rapid and complete healing compared with ranitidine 150mg twice daily or 300mg at night-time, or cimetidine 800 or 1000 mg/day.*

*Patients poorly responsive to treatment with histamine H<sub>2</sub>-receptor antagonists respond well to omeprazole – most ulcers healed within 4 to 8 weeks of omeprazole 40 mg/day therapy. Omeprazole 20 or 40 mg/day has been administered as maintenance therapy for peptic ulcer disease for up to 5.5 years with very few ulcer recurrences.*

*In patients with erosive or ulcerative oesophagitis, omeprazole 20 or 40 mg/day produces healing in about 80% of patients after 4 weeks, and is superior to ranitidine with respect to both healing and symptom relief. Healing rates of > 80% are achieved after 8 weeks in patients with severe reflux oesophagitis unresponsive to H<sub>2</sub>-receptor antagonists. Maintenance therapy with a daily 20mg dose prevents relapse in about 80% of patients over a 12-month period.*

*Omeprazole is considered to be the best pharmacological option for controlling gastric acid secretion in patients with Zollinger-Ellison syndrome. Daily dosages of 20 to 360 (median 60 to 70mg successfully reduce basal acid output to target levels (< 10 mmol/h or < 5 mmol/h in patients with severe oesophagitis or partial gastrectomy) during treatment for up to 4 years.*

*Omeprazole is well tolerated in short term studies (up to 12 weeks); the reported incidence of serious side effects (about 1%) being similar to that seen in patients treated with an histamine H<sub>2</sub>-receptor antagonist. The longer term tolerability of omeprazole has been investigated in patients treated for up to 5.5 years. Slight hyperplasia, but no evidence of enterochromaffin-like (ECL) cell dysplasia or neoplasia or ECL cell carcinoids has been reported. ECL cell carcinoids have been observed in rats after life-long treatment with high doses of omeprazole or ranitidine, or in rats with partial colectomy; the weight of experimental evidence indicates that this is a result of prolonged hypergastrinaemia.*

*Thus, omeprazole is a highly effective alternative to other treatments available for reflux oesophagitis, and duodenal and gastric ulcers – including those conditions poorly responsive to histamine H<sub>2</sub>-receptor antagonists. The potential of omeprazole as prophylaxis for peptic ulcer and reflux oesophagitis is promising and awaits further confirmation of its long term safety. Nevertheless, omeprazole has now reached a stage of its development where it should receive careful consideration by prescribing clinicians as a first-line agent.*

## **Pharmacological Properties**

Omeprazole controls acid secretion by inhibition of gastric H<sup>+</sup>,K<sup>+</sup>-ATPase (the acid pump), the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell. As a weak base, omeprazole concentrates in the acidic milieu of the secretory canaliculi where it is converted by acid to its active sulphenamide derivative. In this form the drug

does not cross cell membranes and is trapped at its site of action. Thus, omeprazole provides an effective and specific means of controlling acid secretion regardless of the nature of the secretory stimulus, and inhibits both basal and stimulated gastric acid secretion.

Gastrin release from antral G cells is stimulated when gastric acid secretion is suppressed, therefore, like other acid inhibitors, omeprazole would be expected to increase plasma gastrin levels. Indeed, short term (< 12 weeks) omeprazole treatment typically increases plasma gastrin levels by 2- to 4-fold - 24-hour levels after a 20mg daily dose are considerably less than those seen in patients with pernicious anaemia, comparable to those achieved with parietal-cell vagotomy, and slightly higher than those seen with ranitidine 150mg twice daily. During longer term therapy, omeprazole 20 or 40 mg/day initially increases plasma gastrin levels, with no further increase noted during extended therapy in most patients.

Studies have shown that the alterations in gastric mucosal morphology observed in rats administered very high doses of omeprazole for prolonged periods represent the effects of hypergastrinaemia occurring in response to profound inhibition of acid secretion. Proliferation of ECL cells in the oxytic mucosa and the development of ECL-cell carcinoids has also been observed in rats with other antisecretory agents (including ranitidine) and following partial corpectomy. The consensus view from published data is that the moderate elevation in plasma gastrin levels observed in clinical studies with therapeutic doses of omeprazole is unlikely to result in clinically significant alterations in gastric morphology (see Tolerability summary).

Placebo-controlled studies in healthy volunteers indicate that omeprazole 40mg daily or more for greater than 4 days significantly reduces aspirin- and naproxen-induced gastric mucosal injury, confirming earlier findings from animal studies.

The bioavailability of omeprazole, administered as enteric-coated granules to limit preabsorption acidic degradation, is about 65% in healthy volunteers.

Peak plasma concentrations and AUC values increase with repeated administration, suggesting that absorption increases and/or first-pass hepatic metabolism becomes saturated. Omeprazole distributes rapidly and widely to extravascular sites ( $V_{\beta} = 0.31 \text{ L/kg}$ ). Although the drug is rapidly eliminated from plasma (mean half-life 0.5 to 1 hour), its antisecretory effect persists for much longer since it is preferentially concentrated in parietal cells where it covalently binds to  $\text{H}^+$ ,  $\text{K}^+$ -ATPase. Elimination is almost entirely by metabolism, followed by primarily urinary excretion. The major plasma metabolites are hydroxyomeprazole and omeprazole sulphone - neither appears to be pharmacologically active.

The disposition of omeprazole does not appear to be altered in patients with renal disease, or in those undergoing haemodialysis. Increased age and liver disease delay plasma clearance of the drug but this does not necessitate dosage adjustment in these patient groups.

## Therapeutic Use

The original review of omeprazole in the Journal established the role of the drug in the short term treatment of duodenal ulcer, and for reducing gastric acid hypersecretion in patients with Zollinger-Ellison syndrome, and demonstrated its potential in gastric ulcer and reflux oesophagitis. In the interim many more clinical trials have been published.

Omeprazole 20 mg/day provides a more rapid response and superior healing rates in patients with duodenal ulcer, and faster relief of associated symptoms, than ranitidine 150mg twice daily or 300mg at night-time, or cimetidine 800 to 1000 mg/day. At these dosages, healing rates were 93% after 4 weeks compared to 83% in patients treated with ranitidine. In patients with gastric ulcer, omeprazole 20 to 40 mg/day was also more effective than ranitidine 150mg twice daily or cimetidine 800 to 1000 mg/day, achieving healing rates of 73 and 91% after 4 and 8 weeks, compared with 62 and 85%, respectively, with ranitidine therapy in a meta-analysis of clinical studies. Omeprazole is highly effective in healing duodenal and gastric ulcers poorly responsive to histamine  $\text{H}_2$ -receptor antagonist treatment, with almost all patients showing complete healing within 4 to 8 weeks at a daily dose of 40mg.

Relapse of healed duodenal ulcers after treatment with omeprazole or  $\text{H}_2$ -receptor antagonists is frequent, and therefore maintenance therapy may be required. Weekend therapy

(20mg administered daily for 3 days/week) appears to provide similar protection against relapse to a 10mg daily dose; 6-month relapse rates ranged from 23 to 29% compared with > 60% in placebo-treated patients. Omeprazole 20 or 40 mg/day administered continuously for up to 5.5 years in a small number of patients provided complete protection against ulcer relapse.

Omeprazole 20, 40 and 60 mg/day is superior to placebo, ranitidine 300 mg/day and cimetidine 1600 mg/day in healing erosive and ulcerative lesions, and relieving symptoms in patients with reflux oesophagitis. After 4 weeks, healing rates were 81 and 6% in patients treated with omeprazole 20 or 40 mg/day and placebo, respectively, and 75 and 23% of patients were free of heartburn after 4 weeks. Relapse in patients with reflux oesophagitis occurs earlier and more frequently than in patients with duodenal ulcer. Patients often require long term treatment to prevent relapse: cumulative remission rates after 12 months were 78 and 15% during continuous and weekend (3 days/week) omeprazole therapy (20mg daily), respectively. Corresponding rates for medium and high dose continuous histamine H<sub>2</sub>-receptor therapy were 38 and 33%, respectively.

In patients with Zollinger-Ellison syndrome a median omeprazole dosage of 60 to 70 mg/day reduces and maintains basal acid output at target levels (< 10 mmol/h or < 5 mmol/h in patients with severe oesophagitis or partial gastrectomy), and also rapidly relieves acid-related symptoms such as heartburn, abdominal pain and diarrhoea during treatment of up to 4 years.

### Tolerability

Omeprazole is well tolerated in short term (< 12 weeks) clinical trials. The incidence of adverse events reported in 19 000 individuals treated in clinical studies did not differ between omeprazole- or placebo-treated patients, and in comparative studies, the incidence ( $\approx$  1% of patients) and spectrum of serious side effects was similar to that associated with H<sub>2</sub>-receptor antagonist therapy. Gastrointestinal symptoms are most frequently reported by patients receiving omeprazole or H<sub>2</sub>-receptor antagonists. Less than 2% of patients have discontinued omeprazole treatment because of adverse events in clinical trials, and there was no relationship between omeprazole dosage and incidence of adverse effects.

During long term (up to 5.5 years) administration of omeprazole at therapeutic doses, no ECL cell dysplasia or neoplasia has been observed.

### Dosage and Administration

A daily 20mg dose is recommended for the treatment of duodenal and gastric ulcer, and reflux oesophagitis, although 40 mg/day may be required in patients with conditions poorly responsive to histamine H<sub>2</sub>-receptor antagonist therapy. Recurrence of reflux oesophagitis has been successfully prevented with daily 20 or 40mg doses while a 10mg daily dose appears promising in patients with duodenal ulcer.

In patients with Zollinger-Ellison syndrome, omeprazole 60 mg/day is recommended initially with individual adjustment to maintain target gastric acid output.

Dosage adjustment is not necessary in elderly patients, or in patients with renal or hepatic impairment.

Control of gastric acid secretion has become the most important strategy in the management of peptic ulcer disease and other acid-related disorders. Omeprazole is a substituted benzimidazole which is structurally and pharmacologically different from the histamine H<sub>2</sub>-receptor antagonists. The drug was first reviewed in the Journal by Clissold and Campoli-Richards in 1986. At that time

its action on hydrogen/potassium adenosine triphosphatase (H<sup>+</sup>,K<sup>+</sup>-ATPase), the acid or proton pump of the parietal cell, was established and its potential importance as a therapeutic agent was emerging. This update focuses on the substantial body of new clinical data which has become available since 1986, and provides an overview of the drug's pharmacological properties.

## 1. Overview of Pharmacological Properties

### 1.1 Mechanism of Action

Results of early studies, subsequently confirmed, indicated that the site of action of omeprazole is in the parietal cell at a point distal to receptors and cAMP, and more particularly that omeprazole specifically binds to vesicular H<sup>+</sup>,K<sup>+</sup>-ATPase in the gastric mucosa (Elander et al. 1986; England et al. 1990; Fryklund et al. 1988a,b). Wallmark et al. (1985) have correlated inhibition of gastric acid secretion with inhibition of H<sup>+</sup>,K<sup>+</sup>-ATPase activity during omeprazole therapy. The action of gastric H<sup>+</sup>,K<sup>+</sup>-ATPase represents the final step in the sequence of events resulting in secretion of hydrochloric acid by the parietal cell. Thus, inhibition of this enzyme represents the most effective and specific means of controlling acid secretion regardless of the nature of the stimulus to secretion. As would be expected with such a mechanism of action, omeprazole has been shown to inhibit both basal and stimulated acid secretion. Omeprazole is a weak base which concentrates in the acid milieu of the secretory canaliculi of the parietal cell where it undergoes rearrangement in acid to its active sulphenamide form. This subsequently reacts with sulphhydryl groups of the acid pump (Beil et al. 1988; Figala et al. 1986; Lindberg et al. 1986, 1990; Morii et al. 1989, 1990b; Wallmark et al. 1985). The effect of omeprazole in regulating the acid pump in isolated hog gastric vesicles has been directly correlated with the rate of sulphenamide formation (Morii et al. 1990a).

While other agents known to inhibit gastric acid secretion also diminish secretion of intrinsic factor, omeprazole was shown in an acute study to have no such effect (Kittang et al. 1985). This finding has now been corroborated in volunteers treated with high oral doses of omeprazole (60 mg/day) for up to 9 days (Festen et al. 1989), and confirms the selective mode of action of omeprazole within the secretory canaliculus of the parietal cell.

Omeprazole had no effect on gastric mucosal histamine levels or histamine methyltransferase activity, or on histamine release during pentaga-

strin stimulation, in patients with duodenal ulcer (Man et al. 1986).

### 1.2 Effects on Gastric Secretion and Plasma Gastrin Levels

Clissold and Campoli-Richards (1986) reviewed data from *in vivo* and *ex vivo* studies in animals which showed omeprazole to be an effective inhibitor of gastric acid secretion – between 2 and 10 times more potent than the histamine H<sub>2</sub>-receptor antagonist cimetidine depending on the route of administration and the experimental model used – and to be equally active regardless of the stimulus applied. Studies in healthy volunteers indicated a prolonged duration of action with omeprazole, and investigations in patients with duodenal ulcer confirmed the greater antisecretory activity of omeprazole compared with cimetidine or ranitidine.

In a number of more recent studies in patients with duodenal ulcer in remission, most of which were aimed at finding the optimum dose of omeprazole for inhibition of acid secretion (e.g. Howden et al. 1986b; McLauchlan et al. 1988; Naesdal et al. 1987; Sharma et al. 1984), doses of less than 20mg daily usually produced only moderate (about 30 to 40%) decreases in basal gastric acid output and showed extensive inter-individual variability. Omeprazole 160 and 200mg given intravenously, in 2 or 3 divided doses for 3 days, was reported to sustain an intragastric pH of greater than 4 in 13 patients with duodenal ulcer in remission (Lind et al. 1986). Intravenous omeprazole may therefore have a potential role in patients with acute upper gastrointestinal bleeding.

Suppression of gastric acid secretion stimulates the release of gastrin, a polypeptide hormone secreted by antral G cells in the stomach, which has 2 major functions: regulation of gastric acid secretion from parietal cells in response to food and pH, and stimulation of mucosal growth in the oxytic or acid-secreting gastric mucosa (Walsh 1990). Thus any mechanism that inhibits gastric acid output – for example, gastric vagotomy or resection of the acid-secreting stomach, pernicious anaemia (non-

antral atrophic gastritis), or administration of acid-inhibiting drugs such as H<sub>2</sub>-receptor antagonists or acid pump inhibitors – would be expected to cause hypergastrinaemia.

The relationship between suppression of gastric acid secretion by omeprazole and plasma gastrin levels has been investigated in healthy volunteers (Lind et al. 1988), patients with duodenal ulcer (Lanzon-Miller et al. 1987a,b; Lind et al. 1990a), and in patients with erosive reflux oesophagitis (Klinkenberg-Knol et al. 1990; Lind et al. 1990b; Lundell et al 1991).

Overall, short term treatment (< 12 weeks) with omeprazole increased fasting plasma gastrin levels by 2- to 4-fold, although up to 10-fold increases have occasionally been reported (Berlin 1991; Clissold & Campoli-Richards 1986; Maton 1991). 24-Hour increases in plasma gastrin levels achieved with omeprazole 20 mg/day are greater than those seen in patients treated with the H<sub>2</sub>-receptor antagonist ranitidine 150mg twice daily, are considerably less than those associated with pernicious anaemia (Lanzon-Miller et al. 1987b), but are comparable to those achieved with parietal-cell vagotomy (Berlin 1991; Lanzon-Miller et al. 1987a; Maton 1991). 24-Hour plasma gastrin profiles maintain a normal circadian rhythm during omeprazole administration but an exaggerated response to food is observed (Lanzon-Miller et al. 1987). Plasma gastrin levels returned to baseline within 2 to 4 weeks of stopping omeprazole therapy.

Plasma gastrin levels, already elevated as a result of previous high-dose (450 to 600 mg/day) ranitidine therapy for  $\geq 3$  months, increased during the first 4 months of omeprazole 40 mg/day maintenance therapy (to 195 ng/L; 4 times normal levels) but showed no further increase with further treatment for 56 months (Brunner et al. 1990). Similar findings have been reported by other groups (Koop et al. 1990b; Lundell et al. 1991), however Jansen et al. (1990) have shown that in some patients plasma gastrin levels continued to rise during prolonged omeprazole treatment. Basal plasma gastrin levels of  $> 500$  ng/L were recorded in 8 of 32 patients with chronic reflux oesophagitis receiving maintenance therapy (20 or 40 mg/day)

for 12 months, but in only 2 patients were levels repeatedly found to be  $> 500$  ng/L (Jansen et al. 1990).

### 1.3 Influence on Gastric Mucosal Morphology

Long term administration to animals of high dosages of omeprazole produced alterations in gastric mucosal morphology. These changes were thought to represent exaggeration of a physiological response related to profound inhibition of gastric acid secretion, with the abolition of the negative feedback of acid on gastrin secretion leading to hypergastrinaemia and reversible hypertrophy of the oxyntic mucosa – the ‘gastrin mechanism’ (Arnold et al. 1986; Axelson et al. 1988; Betton et al. 1988; Blom 1986; Böttcher et al. 1989; Carlsson 1989; Carlsson et al. 1986; Creutzfeldt et al. 1986; Forssell et al. 1986; Koop et al. 1987; Larson et al. 1986; Larsson et al. 1988a,b; Stöckmann et al. 1988; Sundler et al. 1986; Tielemans et al. 1989) – but not of other tissues (Håkanson et al. 1988).

More recently, additional evidence supporting the gastrin mechanism has become available. Several groups of investigators have demonstrated that life-long ( $\geq 2$  years) inhibition of gastric acid secretion in rats following high doses of omeprazole or histamine H<sub>2</sub>-receptor antagonists (including ranitidine) produced significant hypergastrinaemia and was associated with gastric enterochromaffin-like (ECL) cell hyperplasia which may subsequently lead to the development of ECL cell carcinoids in the gastric mucosa (Betton et al. 1988; Carlsson et al. 1990; Havu 1986; Havu et al. 1990; Larsson et al. 1986; Poynter et al. 1985; Ryberg et al. 1989). Other animal studies have reported that hypergastrinaemia produced by continuous infusion of gastrin (5  $\mu$ g/kg/h) for 1 month in the absence of pharmacologically induced acid inhibition (Ryberg et al. 1990a), or as a result of partial gastric corpectomy (which removes about 75% of the acid producing gastric mucosa) [Mattsson et al. 1991a; Ryberg et al. 1990b] resulted in gastric ECL cell hyperplasia within 1 to 3 months. Normal gastrin levels were re-established rapidly after withdrawing high-dose omeprazole therapy in rats (Larsson et

al. 1988a). Another series of experiments, reviewed by Carlsson et al. (1990), show that at follow-up 1 year after discontinuing high-dose omeprazole 14 mg/kg/day (administered for 12 months, at which time all rats showed significant ECL cell hyperplasia), plasma gastrin levels and the incidence of ECL cell hyperplasia did not differ from untreated controls, and there was no evidence of gastric ECL cell carcinoids.

The effect of long term (up to 5.5 years) omeprazole treatment on gastric oxytic mucosal endocrine cells has been studied in patients. In 10 patients with peptic ulcer disease treated with omeprazole 40 to 60mg daily, a significant increase in the volume density of argyrophilic cells in the oxytic mucosa (in association with an increase in plasma gastrin levels) during the first year of therapy was noted, with no further increase in the following year (Lamberts et al. 1988). However, this effect was not confirmed in a larger group of patients ( $n = 18$ ) treated by the same authors for 8 to 16 months and was not observed in antrectomised patients. Several other groups have observed no clinically significant changes in endocrine or parietal cell density, or other cytological parameters, and no dysplastic or neoplastic changes have been observed in patients with duodenal or prepyloric ulcer, or reflux oesophagitis treated with omeprazole 20 to 40 mg/day (Brunner et al. 1990; D'Adda et al. 1991; Helander et al. 1990b; Solcia et al. 1989).

Zollinger-Ellison syndrome (ZES), a disease characterised by profound gastric acid secretion and massive hypergastrinaemia, has been associated with moderate increases in gastric ECL cell density which can lead to ECL cell carcinoid formation in the oxytic mucosa, particularly in the subgroup of patients with multiple endocrine neoplasia type 1 suggesting the likely influence of genetic predisposition (Bardram et al. 1986; Ekman et al. 1985; Helander 1986; Maton et al. 1990; Mignon et al. 1987).

Long term omeprazole treatment (up to 4 years) in patients with ZES did not produce significant changes in the high pretreatment plasma gastrin levels, or any further increase in the number of ECL

cells (Bardram & Stadil 1986; Goldfain et al. 1989; Lehy et al. 1989; Lloyd-Davies et al. 1988; Maton et al. 1989, 1990).

#### 1.4 Prevention of Experimental Gastric Mucosal Damage

Animal studies have conclusively demonstrated that omeprazole provides dose-related protection against mucosal damage induced by a variety of necrotic agents in models of peptic ulcer disease (Hui et al. 1990), including the NSAID naproxen (Oddsson et al. 1990). In placebo-controlled volunteer studies, pretreatment with oral omeprazole  $\geq 40$ mg daily for 4 (Bigard & Isal 1988) or 5 (Daneshmend et al. 1988) days significantly reduced aspirin-induced gastric mucosal injury. Success, as assessed by the 4-point Lanza scale after video endoscopy, was 100% with omeprazole 60mg (vs 7% with placebo) [Bigard & Isal 1988], 92% with 40mg, 67% with 20mg, and 17% with placebo (Bigard 1989). The mechanism underlying this effect is most likely due to the drug's antisecretory action, however this does not appear to be important in its protective action against other necrotising agents since intravenous or intraperitoneal administration of doses which completely inhibit acid secretion did not provide protection (Mattsson 1986; Romano et al. 1989); nor does it appear to be related to bicarbonate secretion, or increased concentrations of prostaglandin or endogenous sulphhydryl compounds (both of which have protective activity) [Romano et al. 1989].

#### 1.5 Other Effects

With the exception of a decrease in antral somatostatin levels (Lamers 1988), omeprazole did not affect 13 other gastrointestinal hormones studied in limited investigations in volunteers (see review by Clissold & Campoli-Richards 1986). Omeprazole does not produce as marked or consistent inhibition of pepsin secretion as it does gastric acid secretion in healthy volunteers or patients with duodenal ulcer (Clissold & Campoli-Richards 1986; Ten Kate et al. 1988). This is not unexpected, given

**Table I.** An overview of pharmacokinetic characteristics of omeprazole (most data from healthy volunteers)**Absorption**

- Bioavailability of enteric-coated granule formulation approximately 65% (relative to a buffered oral solution) [Pilbrant & Cederberg 1985]
- $C_{max}$  after 30 and 60mg enteric-coated granules 0.56 and 1.67 mg/L, respectively (Howden et al. 1984a; Prichard et al. 1985b)
- Doses greater than 40mg result in disproportionate increases in plasma concentrations (Londong et al. 1983; Regårdh et al. 1988; Sharma et al. 1984)
- $C_{max}$  and AUC may increase with repeated administration – AUC increased by 21% (10mg), 69% (20mg) and 182% (40mg) after 5 days (Andersson et al. 1991)
- Absorption is delayed by food but not affected by liquid antacids (Andersson et al. 1990d; Howden & Reid 1988; Pilbrant & Cederberg 1985; Tuynman et al. 1987)

**Distribution**

- $V_d = 0.31 \text{ L/kg}$  (Regårdh et al. 1988, 1990). Reduced in the elderly (Regårdh 1986)
- 95% protein-bound (Regårdh et al. 1988)
- Crosses the placenta in animals (Ching et al. 1986; Regårdh et al. 1988)

**Elimination**

- $t_{1/2} < 1 \text{ hour}$  (Regårdh 1986; Regårdh et al. 1990)
- $t_{1/2}$  increased and total plasma clearance decreased in elderly (Regårdh 1986) and in hepatic disease (Andersson et al. 1986; McKee et al. 1988; Rinetti et al. 1991), but not altered by renal disease (Naesdal et al. 1986) or haemodialysis (Howden et al. 1984b, 1985; Roggo et al. 1990)
- Elimination is almost entirely by metabolism – 6 metabolites have been identified in urine of which the hydroxy and sulphone derivatives are the most important in plasma (Renberg et al. 1989). Major metabolites are inactive (Regårdh 1986)
- 60% of the dose was recovered in urine after 6 hours and 75 to 79% after 96 hours (Regårdh et al. 1988, 1990)
- Faecal excretion (18% of an oral dose) is attributable solely to biliary excretion (Lind et al. 1987)

**Abbreviations:**  $C_{max}$  = peak plasma concentration; AUC = area under the plasma concentration-time curve;  $V_d$  = apparent volume of distribution;  $t_{1/2}$  = elimination half-life.

its mechanism and site of action (section 1.1). However, when compared with the H<sub>2</sub>-receptor antagonist cimetidine, which did not inhibit basal and sham-feed stimulated pepsin secretion, omeprazole had a significant effect on both parameters after 28 days' treatment in refractory duodenal ulcer ( $p < 0.001$ ; Rogers et al. 1990). Ten days of omeprazole 40 mg/day therapy decreased the solid emptying rate in healthy volunteers (half-time 102 min vs 50 min for placebo) without affecting liquid emptying or the lag phase of solid emptying (Rasmussen et al. 1991).

Duodenal bulb acidity was markedly reduced with omeprazole 30 mg/day, particularly under fasting conditions (Bendtsen & Rune 1986) and in patients with reflux oesophagitis, omeprazole 20 to 60mg once daily was more effective than ranitidine 150mg twice daily in normalising oesophageal acidity (Klinkenberg-Knol et al. 1988a; Ruth et al. 1989).

The effects of omeprazole on gastric mucus secretion have not been extensively studied. However, in patients with endoscopic signs of duodenitis, omeprazole 20mg administered daily for 4 weeks reduced the ratio of neutral to total mucoproteins – an index correlating the constituents of gastric mucus with its viscoprotective properties (Guslandi et al. 1990). Omeprazole does not affect thyroid function in humans (Clissold & Campoli-Richards 1986; Howden et al. 1986a; MacGilchrist et al. 1987). When administered as a 60mg dose once daily for 8 days, omeprazole significantly reduced the peak hydrocortisone response to exogenous corticotrophin stimulation in a controlled study in volunteers (Howden et al. 1986c), but the clinical relevance of this effect, if any, remains to be determined.

About 90% of patients with duodenal ulcers show an underlying *Helicobacter pylori*-related gastritis (Rauws et al. 1988). Several investigators have

demonstrated that omeprazole 20 or 40mg administered daily for 28 days cleared *H. pylori* from antral biopsies taken from most patients with duodenal ulcer and/or reflux oesophagitis (Biasco et al. 1989; Mainguet et al. 1989). However, other investigators have shown that clearance is not long lasting (Sharp et al. 1991) and have observed suppression rather than eradication of *H. pylori* (defined as absence of bacterium at least 1 month after cessation of treatment) in patients treated with omeprazole 20 to 40 mg/day (Daw et al. 1990; Rauws et al. 1991; Unge et al. 1989). Omeprazole 40 mg/day plus amoxicillin 750mg twice daily appears to be an effective treatment for eradicating *H. pylori* in patients with antral gastritis (Unge et al. 1989).

### 1.6 Pharmacokinetic Properties

The pharmacokinetic profile of omeprazole was well established in the original review of Clissold and Campoli-Richards (1986), and this section provides an overview only (see table I). Omeprazole has low solubility in water and, because it is labile in acid environments, an enteric-coated formulation has been developed for oral administration to maximise absorption and minimise preabsorption degradation. This overview focuses on the disposition of the oral enteric-coated formulation.

In volunteers and patients with duodenal ulcer or ZES, absorption of omeprazole shows interindividual variability (Lamers et al. 1985; Sharma et al. 1984). Peak plasma concentration and area under the plasma concentration-time (AUC) curve increased after repeated administration of omeprazole in 1 study – increases in AUC of 21, 69 and 182% were reported in volunteers given 10, 20 or 40mg daily doses as enteric-coated granules for 5 days (Andersson et al. 1991). Systemic clearance of a single intravenous omeprazole dose was not altered after 1 month of treatment with oral omeprazole 20 mg/day, whereas AUC values and oral bioavailability increased by 50 and 35%, respectively, in patients with duodenal ulcer (Ching et al. 1991). Taken together, the results of these studies

suggest that during repeated oral administration, absorption of omeprazole may increase or elimination (by first-pass hepatic metabolism) may decrease (Andersson et al. 1990b, 1991; Howden et al. 1984a; Prichard et al. 1985b). The overall effect is a more pronounced increase in antisecretory effect with repeated omeprazole administration than could be anticipated from single dose studies (Andersson et al. 1991).

Plasma elimination half-life is not significantly altered during repeated administration (Andersson et al. 1990b; Howden et al. 1984a; Lind et al. 1986; Londong et al. 1983; Prichard et al. 1985b; Regårdh 1986; Regårdh et al. 1990). Despite its rapid elimination (mean half-life 0.5 to 1 hour), the antisecretory effect of omeprazole is long lasting (see section 1.2) as a result of its strong affinity for the acid pump in parietal cells, and is apparent after plasma concentrations of omeprazole and its metabolites are undetectable (Larsson et al. 1985). While there is no evidence to support a direct relationship between plasma concentrations of omeprazole and the drug's antisecretory effect (see reviews by Cederberg et al. 1985, 1989; Larsson et al. 1985; Skånberg et al. 1985), the degree of gastric acid secretion suppression has been correlated with AUC values (Cederberg et al. 1989) suggesting that the concentration of omeprazole at its site of action determines its antisecretory activity. There is no convenient method for estimating concentrations of omeprazole at its site of action.

## 2. Therapeutic Use

At the time of the original review of omeprazole in the Journal, efficacy was established in the short term treatment of duodenal ulcer and in the long term treatment of patients with ZES (Clissold & Campoli-Richards 1986). Encouraging preliminary results in gastric ulcer and peptic oesophagitis were also available. These results have since been verified, additional investigations have compared omeprazole with the histamine H<sub>2</sub>-receptor antagonists cimetidine and ranitidine, and to a lesser extent famotidine, in the treatment of duodenal or gastric ulcer and reflux oesophagitis, and new data

**Table II.** Double-blind clinical trials comparing omeprazole (O) and ranitidine (R) in patients with endoscopically proven duodenal ulcer

Reference	No. of patients <sup>a</sup>	Dosage (mg)	Ulcer healing rate (% of patients)				Relief of epigastric pain at 2 weeks	
			2 weeks	4 weeks	6 weeks	8 weeks	day	night
Barbara et al. (1987)	61	O 20 od	66	97*	100*		O = R	O = R
	60	R 150 bid	53	85	92			
Bardhan et al. (1986)	33	O 20 od	83*	97*		100		
	36	O 40 od	83*	100*		100		
Cooperative Study Group (1990)	33	R 150 bid	53	82		94	O > R	
	94	O 40 od	68*	99*		100		O > R
	94	R 150 bid	48	88		97		
Gloria et al. (1991)	89	O 20 od	83*	97*			O > R	O > R
	88	R 150 bid	32	74				
Hui et al. (1987)	88	O 10 od	77	95*			O ≥ R	
	90	O 20 od	86	96*				
	89	R 150 bid	63	93				
	131	O 20 od	31	81*			O > R	O > R
Lanza et al. (1991)	132	O 40 od	39*	82*				
	134	R 300 od	24	64				
Marks et al. (1988)	69	O 20 od	78	97				
	66	R 300 od	45	82				
McFarland et al. (1990)	125	O 20 od	79*	91*			O > R	O = R
	122	R 300 od	61	80				
Mulder et al. (1989)	74	O 20 od	63	91				
	75	R 150 bid	65	96				
Sabbatini et al. (1988)	71	O 20 od	66	92	99		O = R	O > R
	74	R 300 od	54	91	96			
	61	O 20 od	66	97*	100*			
	60	R 150 bid	53	85	92			
Valenzuela et al. (1991)	151	O 20 od	42	82*			O = R	O ≥ R
	158	R 150 bid	34	63				

a Number of patients who completed the study.

Abbreviations and symbols: od = once daily; bid = twice daily; O > indicates omeprazole had a statistically superior effect to ranitidine; O ≥ indicates omeprazole tended to have a superior effect; O = indicates omeprazole was comparable to ranitidine. Statistically significant difference compared with ranitidine: \* = p ≤ 0.05.

regarding the efficacy of omeprazole as maintenance therapy have become available.

## 2.1 Duodenal Ulcers

### 2.1.1 Noncomparative, Dose Finding and Placebo-Controlled Studies

The efficacy of omeprazole in the treatment of duodenal ulcer was first demonstrated in noncomparative studies (Bader et al. 1986; Blanchi et al.

1984; Cooperative Study Group 1984; Karvonen et al. 1986; Rinetti et al. 1986; Scandinavian Multi-centre Study 1984). At daily doses of 20 to 40mg omeprazole consistently achieved complete healing of duodenal ulcers in about 80% of patients after 2 weeks and in about 100% of patients after 4 weeks.

Subsequently, a daily dosage of 20mg has been used for the treatment of duodenal ulcer, based on evaluation of peak gastric acid secretion, relief of epigastric pain, consumption of antacids, and

endoscopic examination (Belgian Multicentre Group 1986; Hüttemann et al. 1986; Lanza et al. 1991; Lauritsen et al. 1989a; Miyoshi et al. 1988c; Naesdal et al. 1985; Prichard et al. 1985a; Wong & Lane 1991). Several small studies have demonstrated that there is no apparent benefit from increasing the daily dosage to 30 or 40mg in patients with duodenal ulcer (Humphries & Ekenved 1985; Hüttemann et al. 1986; Röhner et al. 1986; Sharma et al. 1984), but in some clinical trials patients have received this higher dosage.

In a more recent US study, Graham et al. (1990) compared the effects of omeprazole 20 mg/day and placebo in 147 patients with endoscopically documented duodenal ulcer. This multicentre study revealed significant advantages for omeprazole with regard to ulcer healing rates after 2 (41 vs 13%) and 4 (75 vs 27%) weeks, and relief of day and night pain based on per protocol analysis (patients withdrawn or lost to follow-up were excluded). Similar results were obtained using intention-to-treat analysis. The reasons for the lower healing rates achieved with omeprazole in this study are not known.

### 2.1.2 Comparisons with Histamine

#### *H<sub>2</sub>-Receptor Antagonists*

Early clinical trials demonstrated the superiority of omeprazole 20 to 40mg as a daily dose over ranitidine 150mg twice daily or cimetidine 800 to 1000 mg/day, particularly with respect to speed of healing (Clissold & Campoli-Richards 1986). Healing rates after 2 weeks were 72 to 83% in omeprazole recipients, 53 to 59% in ranitidine recipients and 46% in cimetidine recipients. After 4 weeks, omeprazole maintained a higher rate of healing but the difference between treatments appeared less pronounced (92 to 100% with omeprazole vs 82 to 92% with ranitidine and 74% with cimetidine).

More recently, studies have confirmed the more rapid symptomatic response and superior healing rates in patients with duodenal ulcers treated with omeprazole, usually administered as a 20mg daily dose, compared with ranitidine 300 mg/day (table II) or cimetidine 800 to 1200 mg/day (table III). The few studies in which omeprazole 10, 30 or 40

mg/day was used showed little or no difference in healing rates compared with the more typical 20mg daily dose (tables II and III).

A meta-analysis of 10 double-blind clinical studies in which a total of 2225 patients were treated with omeprazole 20mg daily or ranitidine 300mg as a single or twice daily dose provides a quantitative assessment of comparative healing rates (Mulder & Schipper 1990). A statistically significant advantage in favour of omeprazole was observed in ulcer healing rates after 2 (69 vs 53%, p < 0.0001) and 4 (93 vs 83, p < 0.0001) weeks. Matton (1991) reported a similar advantage for omeprazole in a meta-analysis of studies in which treatment was extended to 6 or 8 weeks.

A comparison of omeprazole 20 mg/day and famotidine 40 mg/day in 363 Japanese patients with duodenal ulcer has shown that omeprazole healed ulcers more quickly after 2 (56 vs 33%, p < 0.01) and 4 (88 vs 72%, p < 0.01) weeks, but by 6 weeks the difference was no longer statistically significant (97 vs 91%) [Miyoshi et al. 1988a].

In addition to healing rates, most investigators reported the effect of drug treatment on relief of ulcer-related symptoms (tables II and III). A meta-analysis of published clinical studies shows that 71% of patients treated with omeprazole 20mg daily had complete relief of symptoms within 2 weeks, compared with 58% of ranitidine (300 mg/day) recipients (p < 0.001, n = 2361) [Blum 1990].

Symptomatic improvement (daytime/night-time epigastric pain, heartburn, nausea) was better with omeprazole 20mg once daily compared with ranitidine 300 mg/day after 2 weeks in 450 patients treated for duodenal ulcer (Glise et al. 1991). Diurnal epigastric pain affected 47 and 33% of patients treated with omeprazole and ranitidine, respectively, at inclusion and was reduced to 6 and 11%, respectively, after 2 weeks. The incidence of nocturnal epigastric pain at inclusion and after 2 weeks was almost identical in both groups (35 to 39% and 2%, respectively). An increase in antacid consumption cannot explain the greater pain relief associated with omeprazole – indeed, these patients tended to consume less antacids while under in-

**Table III.** Double-blind clinical trials comparing omeprazole (O) with cimetidine (C) in patients with endoscopically confirmed duodenal ulcer

Reference	No. of patients <sup>a</sup>	Dosage (mg)	Ulcer healing rate (% of patients) <sup>b</sup>			Relief of epigastric pain at 2 weeks	
			2 weeks	4 weeks	6 weeks	day	night
Archambault et al. (1988)	80	O 20 od	58*	84	88	O > C	O = C
	79	C 600 bid	46	80	89		
Bigard et al. (1987)	124	O 20 od	65*	90*		O > C	O = C
	131	C 400 bid	44	79			
Crowe et al. (1989)	98	O 20 od	62*	85*		O > C	O ≥ C
	91	C 800 od	33	61			
Dahlgren et al. (1988)	73	O 30 od	66*	97*	100*	O = C	O = C
	66	C 400 bid	45	84	92		
Harvard Davis et al. (1990)	41	O 20 od <sup>c</sup>	56*	80		O > C	
	38	C 800 od <sup>c</sup>	29	66			
	57	O 20 od <sup>d</sup>	67*	88*		O > C	
	52	C 800 od <sup>d</sup>	36	58			
Hetzler et al. (1986)	40	O 40 od	82*	100*			
	46	C 400 bid	49	80			

a Number of patients who completed the study.

b Based on 'per protocol' analysis (evaluable patients at each assessment time only) except in studies by Archambault et al. and Harvard Davis et al. which used intention-to-treat analysis.

c Patients treated by general practitioners.

d Patients treated as hospital outpatients.

*Abbreviations and symbols:* od = once daily; bid = twice daily; O > indicates omeprazole had a statistically superior effect ( $p < 0.05$ ) to cimetidine; O = indicates omeprazole was comparable to cimetidine; O ≥ indicates omeprazole tended to have a superior effect.

*Statistically significant difference between treatments:* \*  $p \leq 0.05$ .

vestigation (Cooperative Study Group 1990; Crowe et al. 1989; Glise et al. 1991; Gloria et al. 1991; Harvard Davis et al. 1990; McFarland et al. 1990; Marks et al. 1988).

Irrespective of treatment, ulcer healing was delayed in smokers and appeared to be delayed in patients with short (< 5 months) remission time, early onset (before age of 30 years) of ulcer disease, and high gastric acid secretion rates (Hui et al. 1987). In addition, small ulcers (< 10mm) tended to heal more rapidly than larger ones (Cooperative Study Group 1990; Crowe et al. 1989; Dahlgren et al. 1988; Hui et al. 1987; Lauritsen et al. 1988; Mulder et al. 1989).

Despite its effectiveness in the short term healing of duodenal ulcers, omeprazole does not avoid the problem of relapse after withdrawing treatment which has been associated with other antiulcer

agents. This aspect of therapy is discussed in section 2.4.

## 2.2' Gastric Ulcers

Although gastric acid secretion has a known role in the pathogenesis of duodenal ulcer, its importance in the pathogenesis of gastric ulcer is less clear. However, inhibition of gastric acid secretion by histamine H<sub>2</sub>-receptor antagonists has been effective in healing gastric ulcers (see reviews by Brogden et al. 1982; Grant et al. 1989), prompting investigation of omeprazole in this indication.

### 2.2.1 Noncomparative Studies

Noncomparative studies in small numbers of patients have shown that omeprazole administered as a once daily 30 or 40mg dose healed gastric ulcers in 22 to 27% of patients after 2 weeks, 69 to 93% after 4 weeks and 92 to 100% after 6 weeks (Farup

**Table IV.** Double-blind clinical studies comparing omeprazole (O) with H<sub>2</sub>-receptor antagonists in the treatment of patients with endoscopically confirmed gastric ulcer

Reference	No. of patients <sup>a</sup>	Dosage (mg)	Ulcer healing rate (%) of patients			
			2 weeks	4 weeks	6 weeks	8 weeks
<b>Cimetidine (C)</b>						
Bate et al. (1989b)	102	O 20 od		73*		84
	87	C 400 bid		58		75
Lauritsen et al. (1988) <sup>b</sup>	70	O 30 od	54*	81	86	
	69	C 1000 od	39	73	78	
<b>Famotidine (F)</b>						
Miyoshi et al. (1988b)	151	O 20 od	10	59*	83	89
	146	F 20 bid	11	44	77	81
<b>Ranitidine (R)</b>						
Barbara et al. (1987)	80	O 20 od	35*	74*		96*
	80	R 150 bid	9	53		85
Classen et al. (1985)	81	O 20 od	43	81		95
	73	R 150 bid	45	80		90
Cooperative Study Group (1990)	16	O 40 od		81		93
	24	R 150 bid		58		87
Walán et al. (1989)	172 <sup>c</sup>	O 20 od		69*		89
	171 <sup>c</sup>	O 40 od		80*		96*
	169 <sup>c</sup>	R 150 bid		59		85

a Number of patients who completed the study.

b Only patients with prepyloric ulcers.

c Patients with gastric and prepyloric ulcers.

Abbreviations: od = once daily; bid = twice daily. Statistically significant difference: \* p < 0.05 vs H<sub>2</sub>-antagonist treatment.

et al. 1988; Francavilla et al. 1986; Hüttemann 1986). Healing was more rapid in patients with small (< 10mm diameter) ulcers and was not affected by smoking or alcohol consumption (Farup et al. 1988). Symptom relief was rapid – after only 2 weeks almost all patients were free from nocturnal pain, and severe daytime pain had resolved completely after 4 weeks – and antacid consumption decreased by 65% during the first 3 weeks of treatment (Farup et al. 1988).

### 2.2.2 Comparisons with Histamine H<sub>2</sub>-Receptor Antagonists and Other Antiulcer Agents

The first comparative study of omeprazole and ranitidine in patients with gastric ulcer was reported by Classen et al. (1985) and has been followed by several others in which omeprazole 20 to 40 mg/day was compared with ranitidine 150mg twice daily, cimetidine 800 or 1000 mg/day or fa-

motidine 40 mg/day (table IV). With the exception of the earliest study in which omeprazole and ranitidine were of comparable efficacy after 2, 4 and 8 weeks (Classen et al. 1985), all trials have shown more rapid healing with omeprazole. The lack of difference seen between omeprazole and ranitidine in Classen's study may be due to the high percentage of patients who had small (< 8mm diameter) ulcers which tend to respond more rapidly to antisecretory therapy.

In the largest comparative study (Walán et al. 1989), omeprazole was superior to ranitidine both 'globally' (i.e. in all patients, see table IV) and in the subgroup of patients who continued to receive NSAIDs during ulcer therapy. In this latter group (n = 56) healing rates at 4 weeks were 61, 81 and 32% for omeprazole 20mg, 40mg daily, and ranitidine 150mg twice daily, respectively. After 8 weeks respective healing rates were 82, 95 and 53%. Interestingly, healing rates for corporeal and prepy-

loric ulcers were similar, although more rapid healing of prepyloric ulcers could be anticipated because of their close resemblance to duodenal ulcers (Walton et al. 1989). These data, obtained by per protocol analysis, have been reproduced using intention-to-treat analysis. An important point to note is that pairwise comparisons of healing rates revealed statistically significant differences between the two doses of omeprazole (20 and 40 mg/day) at 4 and 8 weeks ( $p = 0.01$ ). Thus, although omeprazole 20 mg/day provides more substantial ulcer healing compared with ranitidine 300 mg/day (Barbara et al. 1987; Walton et al. 1989), it appears that in patients with gastric ulcer raising the dosage to 40 mg/day may provide further improvement (Walton et al. 1989).

While both ranitidine and omeprazole relieve the symptoms of gastric ulceration, omeprazole appeared superior to ranitidine in this regard. After 2 weeks 62, 69 and 55% of patients treated with omeprazole 20 or 40 mg/day, and ranitidine 300 mg/day, respectively, were symptom-free.

A meta-analysis of ulcer healing rates and pain relief in 3 clinical trials (Barbara et al. 1987; Classen et al. 1985; Walton et al. 1989) revealed that 65% of omeprazole recipients were symptom-free within 2 weeks compared to 56% of ranitidine recipients ( $p < 0.05$ ,  $n = 71$ ) [Blum 1990]. Omeprazole was more effective in relieving both diurnal and nocturnal epigastric pain. With regard to ulcer healing rates, omeprazole was more efficacious than ranitidine after 4 (73 vs 62%;  $p < 0.001$ ) and 8 weeks (91 vs 85%,  $p < 0.01$ ).

Similar findings were reported in the few comparisons of omeprazole and cimetidine or famotidine in patients with gastric ulcers. Ulcer healing rates were 73 to 81% and 58 to 73% after 4 weeks of omeprazole or cimetidine treatment, respectively (table IV). Significant differences between omeprazole and cimetidine at 4 weeks were no longer apparent at 6 or 8 weeks.

Endoscopic healing rates were significantly higher in 297 Japanese patients treated with omeprazole 20 mg/day compared with patients receiving famotidine 40 mg/day after 4 (59 vs 44%) but not 8 (89 vs 81%) weeks (Miyoshi et al. 1988b). No

significant difference between groups in symptom improvement was seen in this study, while a significant difference in daytime pain relief for omeprazole over cimetidine after 4 weeks was no longer apparent after 6 or 8 weeks (Bate et al. 1989b; Lauritsen et al. 1988).

Healing of gastric ulcers was delayed in smokers and patients with large ulcers in patients treated with omeprazole or a histamine H<sub>2</sub>-receptor antagonist (Bate et al. 1989b; Classen et al. 1985; Lauritsen et al. 1988; Walton et al. 1989). Age, alcohol consumption, number of ulcers, or history of disease did not influence healing rate (Bate et al. 1989b; Walton et al. 1989).

A preliminary study by Bianchi Porro and associates (1990a) showed that omeprazole 20mg daily was more effective than the cytoprotective agent sucralfate, administered as a 4mg daily dose in patients with NSAID-induced gastric ( $n = 17$ ), duodenal ( $n = 10$ ) or gastric plus duodenal ( $n = 3$ ) ulcers. NSAID therapy was not halted and, after 4 weeks, all patients receiving omeprazole were healed compared with 64% of those receiving sucralfate.

### 2.3 Treatment of Ulcers Poorly Responsive to Histamine H<sub>2</sub>-Receptor Antagonists

Since the aetiology of peptic ulceration is not fully known, the aim of treatment has been to accelerate the healing process rather than to cure underlying causes of the disease. In recent times, a greater understanding of ulcer pathophysiology has favoured control of gastric acid secretion using histamine H<sub>2</sub>-receptor antagonists; however, for reasons as yet unknown, some ulcers show little or no response to this form of therapy and are labelled poorly responsive, refractory, intractable or resistant. For the purpose of this review, poorly responsive is defined as a symptomatic endoscopically proven ulcer that fails to heal after at least 2 months of treatment with cimetidine  $\geq 1$  g/day or ranitidine  $\geq 300$  mg/day (Ponce & Rodrigo 1989; Pounder 1984). Most treatment strategies for poorly responsive peptic ulcers are aimed at continued control of acid secretion using higher doses of hist-

amine H<sub>2</sub>-receptor antagonists, or a more effective antisecretory agent such as omeprazole (Bianchi Porro & Parente 1988).

In the earlier review, Clissold and Campoli-Richards (1986) reported that omeprazole 20 or 40mg once daily for 4 to 8 weeks healed all ulcers in patients with duodenal ( $n = 10$ ), jejunal (3) or gastric (4) ulcers that had not responded to at least 6 months' treatment with histamine H<sub>2</sub>-receptor antagonists (with or without pirenzepine, colloidal bismuth subcitrate or sucralfate) [Tytgat et al. 1985].

Several noncomparative and comparative studies have since confirmed the beneficial effects of omeprazole in patients with duodenal or gastric ulcers poorly responsive to histamine H<sub>2</sub>-receptor antagonist therapy (table V). All patients enrolled in noncomparative investigations received omeprazole 40 mg/day; at this dosage complete healing of duodenal ulcers was seen in almost all patients after 4 weeks. Healing of gastric ulcers appeared to be delayed compared with duodenal ulcers but was achieved in almost all patients after 8 weeks (fig. 1); however, 1 patient with gastric ulcer remained unhealed after increasing the omeprazole dosage to 60 mg/day (Brunner & Creutzfeldt 1989).

Similar healing rates were observed with omeprazole 40 mg/day in comparative studies and after 4 and 8 weeks healing was superior to that achieved in patients continuing therapy with ranitidine 300 or 600 mg/day or cimetidine 800 to 3000 mg/day (table V). In contrast, Delchier et al. (1989) failed to show any significant difference between omeprazole 20 mg/day and ranitidine 300 mg/day with regard to healing rates of duodenal ulcers poorly responsive to histamine H<sub>2</sub>-receptor antagonists. The lower omeprazole dosage and the selection of patients with duodenal ulcers defined as poorly responsive after only 6 weeks of H<sub>2</sub>-receptor antagonist treatment, or a higher than expected response to ranitidine, may explain the apparently reduced efficacy of omeprazole in this study (Bate 1989; Delchier et al. 1989; Savarino et al. 1990).

#### 2.4 Prevention of Ulcer Recurrence

Most patients with peptic ulcers relapse once treatment is withdrawn, regardless of the healing drug used. Relapse occurs within 12 months in most

patients and can be managed by either repeat therapy in which symptomatic relapse is treated, or by daily maintenance (prophylactic) treatment. The effectiveness of maintenance therapy with omeprazole administered as a daily dose, or as weekend therapy (3 days per week) has been compared. Relapse rates in patients with duodenal ulcer after 6 months of treatment with omeprazole 10mg daily, 20mg as weekend therapy, or placebo were 29, 26 and 83%, respectively (Lauritsen et al. 1989b) and 27, 23 and 67%, respectively (Lauritsen et al. 1991).

Preliminary results are available from a multi-centre study in which patients with duodenal ulcers healed with omeprazole 20 mg/day were randomised to receive either omeprazole 10mg once daily ( $n = 37$ ) or weekend therapy with 20 mg/day ( $n = 35$ ) [Bianchi Porro et al. 1990b]. After 6 months, 19% of patients receiving daily maintenance therapy had relapsed compared with 31% of patients receiving weekend therapy.

The effect of omeprazole administered as daily maintenance therapy for up to 5.5 years for prevention of duodenal or gastric ulcers has been evaluated in small groups of patients, all of whom had ulcers previously healed with short term omeprazole treatment (Brunner & Creutzfeldt 1989; Pen et al. 1988; Tytgat et al. 1987). These studies show that patients receiving omeprazole 20 or 40 mg/day remained relapse-free; in some cases relapse occurring during treatment with 20 mg/day was treated successfully by increasing the daily dose to 40mg, and patients subsequently remained relapse-free on the higher dosage.

Several short term studies in which complete healing of acute duodenal or gastric ulcers was achieved with omeprazole or an H<sub>2</sub>-receptor antagonist have been extended to include a treatment-free follow-up of 2 to 12 months (Bardhan et al. 1986; Cooperative Study Group 1990; Danish Omeprazole Study Group 1989; Farup et al. 1989; Glise et al. 1991; Graham et al. 1989; Schiller et al. 1989; Walan et al. 1989). Most of these studies used life-table analysis to assess relapse rates, and therefore adjustment for patient withdrawals and losses to follow-up were accommodated. In most

**Table V.** Clinical studies of omeprazole (O) in patients with duodenal or gastric ulcers poorly responsive to histamine H<sub>2</sub>-receptor antagonist therapy

Reference	No. of patients <sup>a</sup>	Type of ulcer	Previous treatment		Dosage (mg/day)	Ulcer healing rate (% of patients)		
			dosage (mg/day)	duration (months)		2 weeks	4 weeks	8 weeks
<b>Noncomparative studies</b>								
Brunner & Creutzfeldt (1989)	14	DU	R 450; 600	≥ 3	O 40	93	100	
Guerreiro et al. (1990)	53	GU	R 450; 600	≥ 3	O 40	81	94	
Pen et al. (1988)	30 <sup>c</sup>	DU, GU, PU	Various <sup>b</sup>	≥ 2	O 40	80	93	97
	11	DU	NA	> 6	O 40		100 <sup>d</sup>	
	5	GU	NA	> 6	O 40			100
<b>Comparative studies</b>								
Bardhan et al. (1988a)	54	DU	C 80-1000 or R 300	≥ 2	O 40	87*	98*	
	53	DU	C 800-1000 or R 300	≥ 2	C 800-1000 or R 300	39	60	
Bardhan et al. (1988b)	17	DU	C 2000	≥ 3	O 40	82	88	
	17	DU	C 2000	≥ 3	C 2000	59	71	
	9	DU	C 3000	≥ 3	O 40	89	100	
	7	DU	C 3000	≥ 3	C 3000	43	57	
Bardhan et al. (1991)	107 <sup>e</sup>	DU, GU, PU, mixed	C 800-1000	≥ 2	O 40	93	97	
					C 800-1000	43	53	
			R 300	≥ 2	O 40	76	100	
					R 300	33	67	
Delchier et al. (1989)	54	DU	C 800 or R 300	≥ 1.5	O 20	48	80	
	61	DU	C 800 or R 300	≥ 1.5	R 300	46	75	
Delle Fave et al. (1991)	24	DU	C 800 or R 300 or F 40	≥ 3	O 40	83	92	
					R 600	58	83	

a Number of patients who completed the study.

b Ranitidine 300-600 mg/day, famotidine 40-80 mg/day or cimetidine 800 mg/day. Some patients with duodenal ulcer received sucralfate 4 g/day or bismuth citrate 480 mg/day after ≥ 3 months' H<sub>2</sub>-antagonist therapy.

c DU n = 23, GU n = 2, DU plus GU n = 2, PU n = 3.

d Complete healing seen after mean 4.4 weeks.

e DU n = 88, GU n = 3, PU n = 14, mixed n = 2

Abbreviations: DU = duodenal ulcer; GU = gastric ulcer; PU = prepyloric ulcer; R = ranitidine; C = cimetidine; F = famotidine; NA = data not available. Statistically significant difference between treatments: \* p < 0.001.

studies endoscopic examination was done after 3 and 6 months, or if recurrence was suspected.

In the largest study patients previously healed with omeprazole tended to have a more favourable remission pattern compared with those healed with ranitidine; 59% of patients healed with omeprazole

20 (n = 118) or 40 (n = 112) mg/day, and 53% healed with ranitidine 300 mg/day (n = 117) were in remission 6 months after stopping treatment, and 52 vs 48% of patients were asymptomatic (Walsh et al. 1989). Another study reported significantly longer median time in remission (272 vs 175 days,

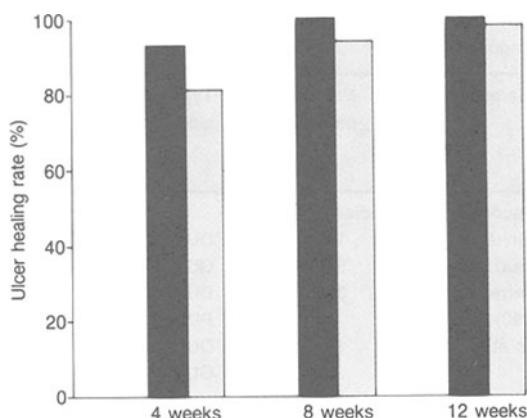
$p < 0.01$ ) during a 12-month treatment-free follow-up of patients whose ulcers were healed with omeprazole 20 mg/day ( $n = 95$ ) compared with those who had received cimetidine 800 mg/day ( $n = 98$ ) [Schiller et al. 1989]. Most of the other investigations reported similar relapse rates in patients healed with omeprazole or an H<sub>2</sub>-receptor antagonist.

Relapse of gastric ulcer was more frequent in smokers, and in patients with a healed prepyloric, rather than corporeal, ulcer regardless of healing treatment (Danish Omeprazole Study Group 1989). In contrast, ulcer size and smoking habit had no significant influence on duodenal ulcer relapse rate (Farup et al. 1989).

## 2.5 Reflux Oesophagitis

Reflux oesophagitis is a common disease characterised by pathological exposure of the distal oesophagus to gastric contents (Pace et al. 1988; Tytgat et al. 1989). Strategies available for treatment of the disease include dietary and postural measures, and pharmacotherapy using antacids, antisecretory agents, prokinetic drugs, and protective agents which may prevent and/or heal mucosal damage resulting from reflux (Pace et al. 1988; Tytgat & Nio 1987; Tytgat et al. 1990). Since the most important factor in the pathophysiology of reflux oesophagitis is prolonged and repeated exposure of oesophageal mucosa to acidic gastric contents, an antisecretory agent such as omeprazole would be expected to have a beneficial effect in patients with this disease.

Since the earlier review other studies have confirmed the superiority of omeprazole over placebo (Dent 1990; Hirschowitz et al. 1989; McCarthy et al. 1986; Whitehead et al. 1989) and several comparative studies have been reported (table VI). A recent placebo-controlled study demonstrated superior endoscopic healing with omeprazole 20 or 40 mg/day compared with placebo (81 vs 6% of patients were healed) after 4 weeks, heartburn was also significantly improved with 75 vs 23% of patients symptom-free after 4 weeks (Dent 1990).



**Fig. 1.** Effect of omeprazole 40mg once daily on healing rates of duodenal (■) and gastric (▨) ulcers in patients who showed no significant improvement during at least 3 months of treatment with high dose ranitidine (450 or 600 mg/day) [after Brunner & Creutzfeldt 1989].

In another phase of this study, healing was improved with omeprazole 40mg compared with 20mg daily doses after 4 weeks (82 vs 70% of patients,  $p = 0.05$ ); this advantage had disappeared by 8 weeks (85 vs 79%, not significant).

Compared with ranitidine 150mg twice daily or cimetidine 400mg 4 times daily, a single daily dose of omeprazole 20 to 60mg provided more rapid and frequent healing (re-epithelialisation) of ulcerative and erosive lesions, and more pronounced symptomatic relief, even at the lowest (20mg) dosage used (fig. 2).

Meta-analysis of 3 comparative studies in a total of 437 patients revealed a 4-week healing rate of 75% in patients treated with omeprazole 20mg daily compared with 45% in patients given ranitidine 150mg twice daily ( $p < 0.001$ ); corresponding rates after 8 weeks were 90 and 58%, respectively (Blum 1990).

Some of the studies summarised in table VI also analysed healing rates according to the pretreatment severity of oesophagitis. Omeprazole was markedly superior to ranitidine in all grades of oesophagitis including patients with severe disease (Havelund et al. 1988; Sandmark et al. 1988; Vantropen et al. 1988) and those with Barrett's oeso-

**Table VI.** Double-blind studies comparing omeprazole (O) and ranitidine (R) or cimetidine (C) in patients with reflux oesophagitis

Reference	No. of patients <sup>a</sup>	Dosage (mg)	Healing rate (%) of patients <sup>b</sup>		Rate of resolution of symptoms (%) of patients <sup>c</sup>	
			4 weeks	8 weeks	O	R or C
<b>Cimetidine</b>						
Bate et al. (1989a)	104	O 20 od	56*	71*	46*	22 (overall)
	94	C 400 qid	26	35	66*	41 (overall, 8w)
Dehn et al. (1990)	31	O 40 od	57*	74*	92*	53 (heartburn)
	36	C 400 qid	29	23		
<b>Ranitidine</b>						
Havelund et al. (1988)	75	O 40 od	77*	91*	86*	48 (regurgitation)
	67	R 150 bid	39	60	85*	47 (dysphagia)
Klinkenberg-Knol et al. (1987)	25	O 60 od	76*	88*	92*	65 (overall, 2w)
Sandmark et al. (1988)	42	O 20 od	67*	85*	77*	36 (heartburn)
	48	R 150 bid	31	50	73*	46 (overall)
Vantrappen et al. (1988)	25	O 40 od	85*	96*	85*	24 (heartburn)
	25	R 150 bid	40	52	62	12 (overall)
Zeitoun et al. (1989)	61	O 20 od	81*	95*	74*	33 (overall)
	61	R 150 bid	45	66	82*	48 (overall, 8w)

a Number of patients who completed the study.

b Based on 'per protocol' analysis (evaluable patients at each assessment time only) except in studies by Bate et al. (1989a), Dehn et al. (1990), and Klinkenberg-Knol et al. (1987) which used intention-to-treat analysis.

c Rate of symptom resolution at 4 weeks unless otherwise indicated.

*Abbreviations and symbols:* od = once daily; bid = twice daily; qid = 4 times daily; w = weeks. *Statistically significant difference between treatments:* \* p < 0.05.

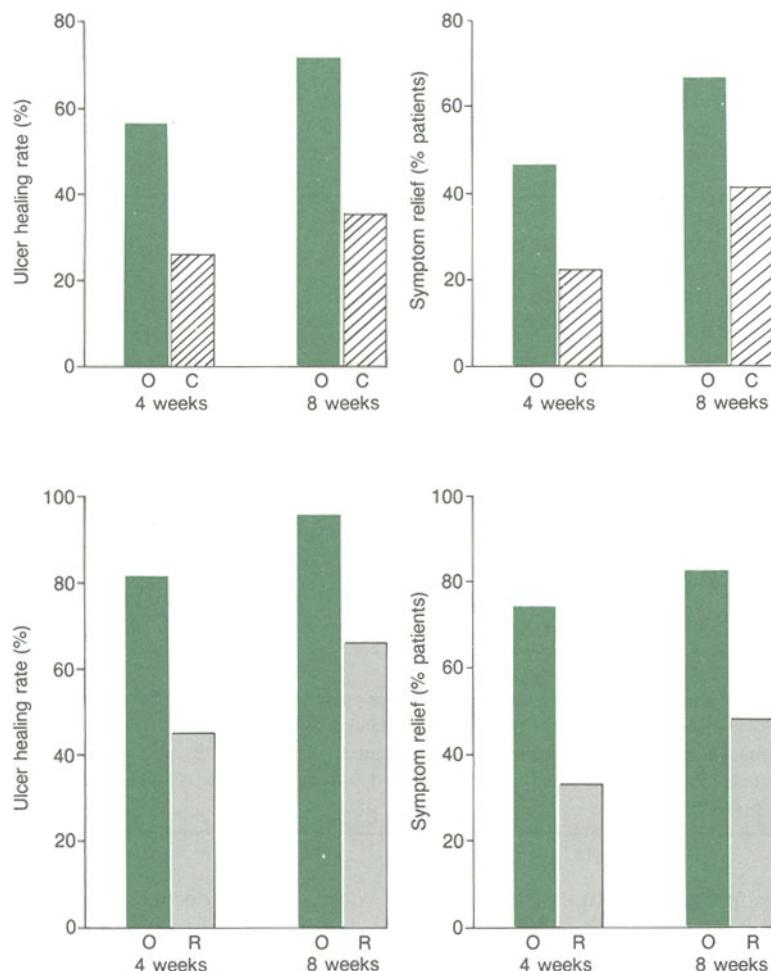
phagus and/or oesophageal strictures (Bardhan et al. 1990; Koop et al. 1990; Sandmark et al. 1988).

Several groups have demonstrated the benefit of omeprazole in patients with severe reflux oesophagitis unresponsive to high dose ranitidine (300 to 900 mg/day) or cimetidine (800 to 3200 mg/day) administered for at least 3 months (table VII). When administered as a single 40mg daily dose, omeprazole healed more than 80% of patients after 8 weeks, and provided complete relief of symptoms in > 60% of patients (table VII). The corresponding healing rate in a group of patients who continued to receive ranitidine 600 mg/day was 38% (fig. 3).

### 2.5.1 Prevention of Reflux Oesophagitis Recurrence

Long term therapy is warranted in the majority of patients with reflux oesophagitis since relapse is frequent irrespective of the healing treatment. In-

deed, relapse occurs earlier and more frequently after withdrawal of healing treatment in patients with reflux oesophagitis compared with those with duodenal ulcer. Hetzel et al. (1988) reported recurrence of erosive or ulcerative oesophagitis in 82% of 107 healed patients 6 months after discontinuing omeprazole treatment. In this study relapse was not influenced by initial omeprazole dosage, grade of oesophagitis or cigarette use. The investigations of omeprazole administered as maintenance therapy in this difficult therapeutic area suggest that a daily dosage of 20mg prevents recurrence of oesophageal symptoms in more than 60% of patients during follow-up of up to 12 months; relapsed patients were re-healed and subsequently maintained on a higher (40 mg/day) omeprazole dose (Bardhan et al. 1990; de Bruyne et al. 1990; Dent 1990; Dent et al. 1989; Klinkenberg-Knol et al. 1988b; Koop et al. 1990a). Cumulative remis-



**Fig. 2.** Ulcer healing rate and relief of overall symptoms in patients with reflux oesophagitis after 4 and 8 weeks' treatment with omeprazole (O) 20 mg/day ( $n = 104$ ) or cimetidine (C) 1600 mg/day ( $n = 94$ ), and omeprazole 20 mg/day ( $n = 61$ ) or ranitidine (R) 300 mg/day ( $n = 61$ ). All between-group comparisons were statistically significant ( $p < 0.001$ ) [after Bate et al. 1989b; Zeitoun et al. 1989].

sion rates at 12 months reported by Bardhan et al. (1990) demonstrate the increased efficacy of a daily 20mg dose compared with 20mg at weekends only: remission rates were 78 and 15% during daily maintenance and weekend maintenance treatment, respectively, compared with 38 and 33% in patients receiving daily maintenance therapy with medium dose (cimetidine 1600 mg/day, ranitidine 450 mg/day) or high dose H<sub>2</sub>-receptor antagonists (cimetidine 3200 mg/day, ranitidine 900 mg/day). Similarly Dent (1990) and Lundell et al. (1991) re-

ported that 89 and 67% of patients, respectively, remained in remission with omeprazole 20 mg/day over 12 months compared with 25 and 10%, respectively, of those given ranitidine 150mg twice daily.

Endoscopic and symptomatic evidence of recurrent oesophagitis has been noted 10 days after withdrawal of long term (up to 4 years) omeprazole maintenance therapy (20 to 60 mg/day) in patients with H<sub>2</sub>-receptor antagonist-resistant reflux oesophagitis (Klinkenberg-Knol et al. 1990).

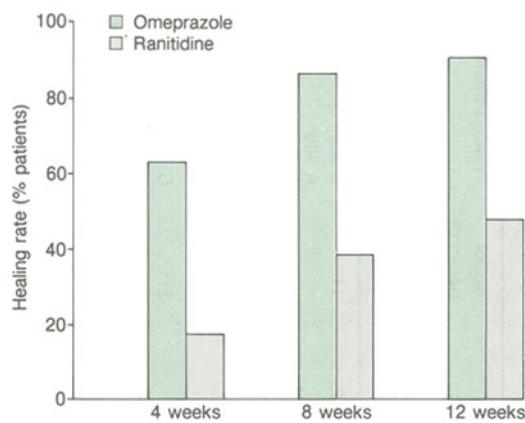
## 2.6 Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome is a rare syndrome characterised by extreme hypersecretion of gastric acid and intractable ulceration (Jensen et al. 1986). With the exception of patients with advanced metastatic disease, symptoms in virtually all patients are the result of excessive gastric acid secretion. Consequently therapy is aimed at controlling acid secretion, historically by partial or total gastrectomy, but more recently through agents such as histamine H<sub>2</sub>-receptor antagonists or omeprazole (Bonfils & Mignon 1988). The effectiveness of omeprazole therapy in patients with Zollinger-Ellison syndrome has been assessed by endoscopic examination, symptomatic relief and control of gastric acid secretion. Although gastric acid secretion is variable in these patients, a reduction in basal acid output to < 10 mmol/h (or < 5 mmol/h in patients with severe oesophagitis or in those who have had a partial gastrectomy) for the hour prior to the next dose is generally accepted as a good indicator of long term efficacy (Maton et al. 1988).

Early noncomparative studies and case reports showed that omeprazole (in dosages up to 180 mg/day) produced rapid and pronounced inhibition of gastric acid secretion, with marked symptomatic improvement and ulcer healing, in patients who showed little or no response to standard doses of cimetidine or ranitidine with or without concomitant pirenzepine (see, for example, Blanchi et al. 1982; Lamers et al. 1984; McArthur et al. 1985; Mignon et al. 1984; Vezzadini et al. 1984). In these studies patients who received omeprazole 20 to 160 mg/day for up to 19 months were endoscopically healed and symptom-free within 1 to 2 weeks and remained so during longer term therapy with dosage adjustment when necessary (Lamers et al. 1984; McArthur et al. 1985). Basal acid output remained inhibited (by > 80%) during the 24 hours following omeprazole withdrawal, and by > 50% within 48 hours (McArthur et al. 1985).

More recent studies using a median omeprazole dosage of 60 to 70 mg/day (daily dose range 20 to 360mg) have confirmed these earlier findings and

extended their application to longer (4 years) treatment periods (Bardram & Stadil 1986, 1989; Cadranel et al. 1989; Delchier et al 1986; Hirschowitz et al. 1988; Lloyd-Davies et al. 1988; Maton et al. 1989). Basal acid output was reduced to < 10 mmol/h in most patients within the first day of treatment and was accompanied by rapid relief of acid-related symptoms (heartburn, abdominal pain, and diarrhoea) in almost all patients. During longer term treatment, dosage was adjusted primarily on the basis of basal acid output. In some patients, the initial omeprazole dose could be reduced without compromising control of acid secretion whereas others required an increase in dose after 6 to 48 months of therapy (Bardram & Stadil 1986, 1989; Delchier et al. 1986; Lloyd-Davies et al. 1988; Maton et al. 1989). Patients who responded poorly to single daily doses of omeprazole 40 to 120mg were successfully controlled when the dose was divided and given every 12 hours (Lloyd-Davies et al. 1988; Maton et al. 1989). The variation between patients' response to long term omeprazole makes initial individual monitoring of therapy essential. On balance it appears that 1 dosage adjustment is often sufficient to achieve control of basal acid output, thereafter adjustment may be infrequent or unnecessary. There is no evidence of tachyphylaxis de-



**Fig. 3.** Healing rates in 98 patients with reflux oesophagitis poorly responsive to ≥ 3 months' cimetidine ≥ 1200 mg/day or ranitidine ≥ 300 mg/day after 4, 8 and 12 weeks of omeprazole 40mg once daily (n = 51) or ranitidine 300mg twice daily (n = 47) [after Lundell et al. 1990].

**Table VII.** Clinical trials of omeprazole (O) in patients with reflux oesophagitis poorly responsive to histamine H<sub>2</sub>-receptor antagonist therapy

Reference	No. of patients <sup>a</sup>	Previous treatment		Dosage (mg/day)	Healing rate (% of patients)			Complete symptom relief (% of patients)		
		dosage (mg/day)	duration (months)		4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
Bardhan et al. (1990)	41	C 3200 or R 900	≥ 3 ≥ 3	O 40	73	91			60	
Dent et al. (1989)		C 800-2400 or R 300-900	10 (median)	O 40			85			
Koop et al. (1990)	61	R ≥ 300	≥ 3	O 40	48	80	92	63	84	92
Lundell et al. (1990)	51	C ≥ 1200 or R ≥ 300	≥ 3 ≥ 3	O 40 R 600	63 17	86 38	90* 47	86* 32		
Marciano-D'Amore et al. (1990)	25 <sup>b</sup>	H <sub>2</sub> RA	≥ 9	O 40	80 <sup>c</sup>	96 <sup>c</sup>		84 <sup>d</sup>	96 <sup>d</sup>	

a Number of patients who completed the study.

b Retrospective study.

c First follow-up endoscopy after 30 to 79 days, second after an additional 1 to 2 months.

d Average time to first and second clinic visits 41 and 65 days, respectively.

Abbreviations: C = cimetidine; R = ranitidine; H<sub>2</sub> RA = H<sub>2</sub>-receptor antagonists (unspecified). Statistically significant difference between treatments: \* p < 0.0001.

veloping during long term omeprazole treatment (Lloyd-Davies et al. 1988).

Reflux oesophagitis in patients with Zollinger-Ellison syndrome has not previously been well studied. However, Miller et al. (1990) have reported that in a series of 122 patients, 45% had oesophageal symptoms (dysphagia and/or heartburn) and 43% had endoscopic abnormalities of the oesophagus; these patients also had symptoms of gastric or duodenal ulcer. Symptoms of reflux oesophagitis appear to be more difficult to resolve than those associated with ulceration since inhibition of basal acid output to < 10 mmol/h with omeprazole therapy resolved ulcer symptoms in all patients but only 73% of patients with reflux oesophagitis were symptom-free. Patients with the most intractable disease required intensive suppression of gastric acid secretion (to < 1 mmol/h) before oesophageal symptoms resolved.

Intravenous omeprazole administered pre- and postoperatively as a 60mg bolus every 12 hours effectively reduced gastric acid output in most patients with Zollinger-Ellison syndrome undergoing surgery, thus providing an alternative to continuous infusion of high doses of an H<sub>2</sub>-receptor antagonist which has been the mainstay for controlling gastric hypersecretion in such patients (Vinyayek et al. 1990).

### **3. Tolerability**

#### **3.1 Short Term Tolerability**

The short term (2 to 12 weeks) tolerability of omeprazole has been well established in clinical trials (for reviews see Clissold & Campoli-Richards 1986; Nelis 1989; Sölvell 1989, 1990).

A review of more than 19 000 individuals treated in clinical trials has shown that during short term treatment (2 to 12 weeks) the incidence and severity of adverse events did not differ between patients treated with omeprazole or placebo (Sölvell 1990). In comparative clinical studies the incidence of serious adverse events (defined by the authors as any event which poses a definite hazard or handicap to the patient irrespective of a causative relationship to drug treatment) was similar

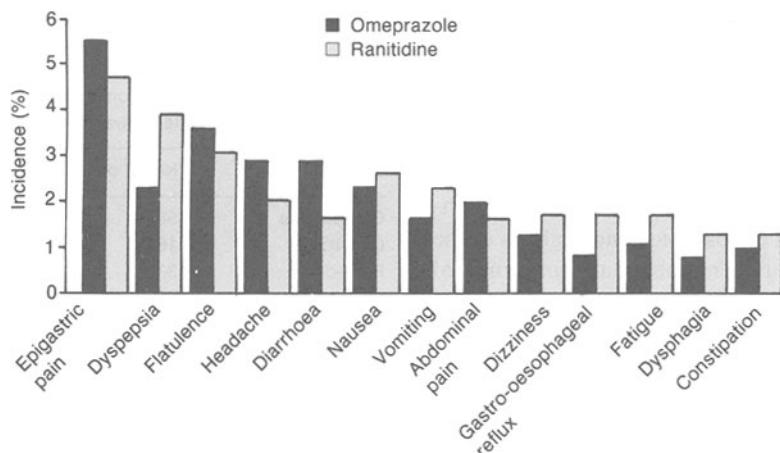
**Table VIII.** Incidence of serious adverse effects (defined as any event which constitutes a definite hazard or handicap to the patient, irrespective of any relationship to drug treatment) reported in studies comparing omeprazole with placebo or H<sub>2</sub>-receptor antagonists (after Sölvell 1990)

Drug treatment	No. of patients	Incidence (%)
Omeprazole	5679	1.1
Cimetidine	1638	1.4
Ranitidine	3324	0.8
Placebo	248	4.0

(about 1%) for omeprazole, cimetidine and ranitidine (table VIII). The pattern of adverse events was also similar in patients receiving omeprazole or an H<sub>2</sub>-receptor antagonist with gastrointestinal symptoms (epigastric pain, dyspepsia, flatulence, diarrhoea, nausea and vomiting) being among the most frequently reported (fig. 4). Isolated reports of skin rash, including occasional lichenoid eruptions (Lee et al. 1989; Sharma et al. 1984), peripheral neuropathy (Sellapah 1990), gynaecomastia (Santucci et al. 1991), and haemolytic anaemia (Marks et al. 1991) have been reported in patients treated with omeprazole.

In dose finding studies, no relationship between omeprazole dose (10 to 60mg) and incidence of adverse events has been established. Incidence rates appear similar in elderly (> 65 years) and younger patients (Sölvell 1989, 1990). Withdrawal from treatment because of adverse events has been necessary in less than 2% of patients treated in clinical trials (Sölvell 1990).

No significant changes in transaminase levels or other indicators of hepatic function, renal function, or thyroid hormone levels have been associated with short term omeprazole use. Furthermore, omeprazole does not appear to cause significant changes in haematological parameters, electrolyte levels or concentrations of intestinal peptides or other hormones, or clinically significant changes in blood pressure, heart rate or ECG (Nelis 1989; Sölvell 1989).



**Fig. 4.** Incidence (%) of adverse effects reported in 1369 patients treated with omeprazole 20 to 40 mg/day and in 1041 patients treated with ranitidine 300 mg/day in comparative clinical studies (after Sölvell 1990).

### 3.2 Long Term Tolerability

The tolerability of omeprazole during long term treatment is of considerable interest since there is increasing evidence that maintenance therapy will prevent ulcer and oesophagitis recurrence in most healed patients. In clinical trials of up to 4 years' duration in which patients received omeprazole 20 to 40 mg/day, the profile of adverse effects was similar to that seen in short term studies (Lloyd-Davies et al. 1988; Maton et al. 1989; section 3.1). Most adverse effects were minor and infrequent and included constipation, diarrhoea, dysphagia, vomiting and migraine.

Data from more than 2000 patients treated with omeprazole 20 to 40 mg/day for > 6 months (in some instances for up to 5.5 years) show only moderate increases in plasma gastrin levels with no evidence of gastric ECL cell dysplasia or neoplasia (Creutzfeldt & Lamberts 1991; Lloyd Davies et al. 1988; Lundell et al. 1991; Maton et al. 1989; Sölvell 1990). Indeed, in biopsies taken from 248 patients after at least 11 months of omeprazole 20 mg/day, no drug-related changes in gastric endocrine cells were noted (Sölvell 1990). Creutzfeldt and Lamberts (1991) reported slight ECL cell hyperplasia in patients treated with omeprazole for

more than 4 years but all stages of hyperplasia were already present in pretreatment biopsies.

Patients with Zollinger-Ellison syndrome (characterised by profound acid secretion and hypergastrinaemia) may develop gastric ECL cell hyperplasia and ECL cell carcinoids, particularly in patients with multiple endocrine neoplasia type 1 (see section 1.3). Omeprazole does not appear to cause further hyperplasia or gastric ECL cell carcinoid formation in these patients after treatment of up to 4 years. Focal hyperplasia of argyrophil cells has been observed in patients with chronic gastric ulcer with no pronounced hypergastrinæmia who had never received treatment with an acid pump inhibitor or a histamine H<sub>2</sub>-receptor antagonist (Havu et al. 1991) suggesting a link between chronic atrophic gastritis and focal hyperplasia of argyrophil cells in such patients (Havu et al. 1991; Maaroos et al. 1985).

Despite intensive speculation, several lines of evidence (including mutational assays in bacteria, mutation and chromosome damage tests on mammalian cells *in vitro*, chromosome damage tests in mouse bone marrow and erythroid precursor cells exposed *in vivo*, and DNA damage assays in the nuclei of rat liver cells exposed to omeprazole *in vivo*) indicate that neither omeprazole nor its me-

tabolites have genotoxic potential (Evans 1990; Sachs et al. 1990). In addition, an *in vivo* study that was purported to show that omeprazole induced unscheduled DNA synthesis (a measure of possible drug-induced DNA damage) in rat gastric mucosa (Burlinson 1989) has been shown to be technically flawed, and without scientific validity by various groups of investigators (Helander et al. 1990a; Larsson et al. 1991; Scott et al. 1990; Wallmark et al. 1990; Wright 1990; Wright & Goodlad 1990).

#### **4. Drug Interactions**

Omeprazole interferes with a specific enzyme within the cytochrome P450 system in the liver (Andersson 1991) and inhibits the metabolism of some drugs – for example the R-isomer of warfarin (Sutfin et al. 1989), diazepam and phenytoin (Andersson et al. 1990a,c; Gugler & Jensen 1984, 1985; Prichard et al. 1987) – but not others such as propranolol (Henry et al. 1987), the S-isomer of warfarin (Sutfin et al. 1989) or theophylline (Gugler & Jensen 1987). Thus, the ability of omeprazole to interfere with the metabolism of other drugs appears to be limited, and reports to date are of little clinical relevance (Andersson et al. 1991).

#### **5. Dosage and Administration**

A daily 20mg dose of omeprazole administered in the morning is recommended for the treatment of active gastric or duodenal ulcers, or reflux oesophagitis. A dosage of 40 mg/day may be required in patients with ulcers or reflux oesophagitis poorly responsive to histamine H<sub>2</sub>-receptor antagonist therapy. Treatment should be continued until healing occurs, usually within 2 to 4 weeks for duodenal ulcers and 4 to 8 weeks for gastric ulcers and reflux oesophagitis. A 20 or 40mg daily dose has been used successfully as maintenance therapy to prevent recurrence in patients with reflux oesophagitis or severe peptic ulcer disease and 10mg daily doses appear promising in preventing relapse of duodenal ulcer.

A starting dosage of 60mg daily is recommended in patients with Zollinger-Ellison syn-

drome; this may be adjusted as necessary to maintain gastric acid secretion below 10 mmol/h (or < 5 mmol/h if the patient has severe oesophagitis or has had a partial gastrectomy) for the hour preceding the next dose. Doses greater than 80 mg/day may be divided and given at 12-hourly intervals to improve efficacy.

Dosage adjustment is not necessary in patients with impaired renal or hepatic function, or in elderly patients. Insufficient data are currently available for dosage recommendations in children.

#### **6. Place of Omeprazole in Therapy**

The success of gastric acid suppression by histamine H<sub>2</sub>-receptor antagonists in the treatment of peptic ulcer disease and other disorders of acid secretion is now well established. Not surprisingly, this has prompted a search for longer acting agents with improved efficacy. Omeprazole is the first of a new class of drugs, the acid pump inhibitors, which inhibit the terminal stage in the acid secretory process and thus, unlike other antisecretagogues, control gastric acid secretion irrespective of the primary stimulus.

Since the initial review of the drug was published in the Journal in 1986, a more complete assessment of omeprazole in the treatment of acute duodenal and gastric ulcers, and reflux oesophagitis, including those conditions poorly responsive to histamine H<sub>2</sub>-receptor antagonist therapy, and in the long term treatment of Zollinger-Ellison syndrome, has become possible. Also, in the interim the base of clinical experience has widened to include the use of omeprazole as maintenance therapy in patients with duodenal or gastric ulcer, or reflux oesophagitis.

There is no doubt that omeprazole provides rapid and consistent healing of duodenal and gastric ulcers, and relief of associated symptoms, when administered as a once-daily 20mg dose. Healing rates of about 70% are reported after 2 weeks in patients with duodenal ulcer; after 4 weeks about 95% of patients are healed. Similar but slightly delayed healing rates are seen in patients with gastric ulcer. These healing rates are superior to those

achieved with the histamine H<sub>2</sub>-receptor antagonists ranitidine, cimetidine and famotidine.

Ulcer relapse is common in patients irrespective of the healing therapy once treatment is withdrawn. During maintenance therapy with omeprazole 20 or 40 mg/day, relapse has been prevented in most patients with duodenal or gastric ulcer treated for up to 5.5 years. Initial results from other studies have demonstrated the comparable efficacy of omeprazole 10 mg/day, or a 20mg dose administered for 3 days per week (weekend therapy), as maintenance treatment in patients with duodenal ulcer. Further investigation into the use of omeprazole as prophylaxis against duodenal ulcer recurrence is ongoing to corroborate these encouraging preliminary findings.

Healing of erosive and ulcerative lesions, and relief of acid-related symptoms, in patients with reflux oesophagitis is more rapid and frequent with omeprazole than with the H<sub>2</sub>-receptor antagonists, ranitidine or cimetidine. Substantial differences between the efficacy of these agents are apparent in patients with all grades of reflux oesophagitis. Healing rates of about 70 to > 90% have been achieved after 8 weeks of omeprazole therapy; corresponding rates are about 30 to 35% with cimetidine and 40 to 60% with ranitidine therapy. Because of the high rate of relapse in patients with reflux oesophagitis, long term therapy is often required. Maintenance therapy with H<sub>2</sub>-receptor antagonists does not prevent recurrence of reflux oesophagitis. Clinical trials have shown that omeprazole 20 mg/day prevents recurrence of reflux oesophagitis in about 70 to 90% of patients over 12 months.

Omeprazole is highly effective in patients with Zollinger-Ellison syndrome, and has been used successfully as maintenance therapy (for up to 4 years) in these patients. Most patients ( $\approx$  80%) achieve target basal acid output (< 10 mmol/h, or < 5 mmol/h in patients with severe oesophagitis, or partial gastrectomy) within a day of beginning omeprazole treatment but in some patients it may take several days to control acid secretion because extreme acid hypersecretion reduces the bioavailability of the drug (personal communication, P.

Maton). Omeprazole has been used successfully to control acid secretion in patients resistant to treatment with H<sub>2</sub>-receptor antagonists and is currently the best pharmacological option available for the treatment of patients with Zollinger-Ellison syndrome.

The short term safety of omeprazole has been established in over 19 000 individuals treated in clinical studies. The overall incidence of serious adverse events in clinical trials (about 1%) is similar to that reported for the H<sub>2</sub>-receptor antagonists, ranitidine and cimetidine, in comparative studies. Concerns regarding the long term safety of omeprazole which were based on the observation that gastric ECL cell hyperplasia and subsequent ECL cell carcinoids developed in rats treated with high doses of omeprazole for long periods have now been intensively investigated. The accumulated body of evidence strongly indicates that the development of gastric ECL cell carcinoids in the rat gastric mucosa is a result of prolonged (life-long) hypergastrinaemia which can be achieved surgically (by partial gastric corpectomy) or pharmacologically (by administration of high-dose omeprazole or ranitidine for prolonged periods). Although the overwhelming balance of opinion favours the 'gastrin mechanism' (Creutzfeldt & Lamber 1991) contrary arguments have been presented.

Data from clinical trials in which patients received omeprazole (generally 20 to 40 mg/day but in some instances as high as 360 mg/day) for up to 5.5 years have not shown any significant changes in gastric mucosal morphology. Furthermore, an attempt to demonstrate that omeprazole has a direct genotoxic effect has been refuted.

In conclusion, omeprazole represents a major advance in the treatment of reflux oesophagitis and duodenal and gastric ulcers – including those conditions poorly responsive to histamine H<sub>2</sub>-receptor antagonist therapy. Its use as prophylaxis in these conditions is encouraging and warrants further study. In Zollinger-Ellison syndrome omeprazole is extremely effective and is the best pharmacological option available to clinicians. The long term tolerability of omeprazole is being thoroughly in-

vestigated and evidence accumulated over recent years indicates no need to limit its use on the basis of clinical safety. While many factors are involved in selecting a drug for treatment and prophylaxis of peptic ulcer and related disorders, omeprazole should receive careful consideration as a potential first-line therapy.

## References

- Andersson T. Omeprazole drug interaction studies. *Clinical Pharmacokinetics* 21: 195-212, 1991
- Andersson T, Andrén K, Cederberg C, Edvardsson G, Heggelund A, et al. Effect of omeprazole and cimetidine on plasma diazepam levels. *European Journal of Clinical Pharmacology* 39: 51-54, 1990c
- Andersson T, Andrén K, Cederberg C, Heggelund A, Lundborg P, et al. Bioavailability of omeprazole as enteric coated (EC) granules in conjunction with food on the first and seventh days of treatment. *Drug Investigation* 2: 184-188, 1990d
- Andersson T, Andrén K, Cederberg C, Lagerstrom D-O, Lundberg P, et al. Pharmacokinetics and bioavailability of omeprazole after single and repeated oral administration in healthy subjects. *British Journal of Clinical Pharmacology* 29: 557-563, 1990b
- Andersson T, Cederberg C, Edvardsson G, Heggelund A, Lundborg P, et al. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clinical Pharmacology and Therapeutics* 47: 79-85, 1990a
- Andersson T, Cederberg C, Heggelund A, Lundborg P. The pharmacokinetics of single and repeated once-daily doses of 10, 20 and 40mg omeprazole as enteric-coated granules. *Drug Investigations* 3: 45-52, 1991
- Andersson T, Olsson R, Skånberg I, Heggelund A, Johnsson C, et al. Pharmacokinetics of omeprazole in patients with liver cirrhosis. *Acta Pharmacologica et Toxicologica* 59 (Suppl. 5): 203, 1986
- Archambault AP, Pare P, Bailey RJ, Navert H, Williams CN, et al. Omeprazole (20mg daily) versus cimetidine (1200mg daily) in duodenal ulcer healing and pain relief. *Gastroenterology* 94 (Pt 1): 1130-1134, 1988
- Arnold R, Koop H, Schwarting H, Tuch K, Willemer B. Effect of acid inhibition on gastric endocrine cells. *Scandinavian Journal of Gastroenterology* 125 (Suppl.): 15-18, 1986
- Axelson J, Håkanson R, Rosengren E, Sundler F. Hypergastrinemia induced by acid blockage evokes enterochromaffin-like (ECL) cell hyperplasia in chicken, hamster and guinea-pig stomach. *Cell and Tissue Research* 254: 511-516, 1988
- Bader J-P, Modigliani R, Soule JC, Delchier JC, Morin R, et al. An open trial of omeprazole in short-term treatment of duodenal ulcer. *Scandinavian Journal of Gastroenterology* 21 (Suppl. 118): 177-178, 1986
- Barbara L, Blasi A, Cheli R, Corinaldesi R, Dobrilla G, et al. Omeprazole vs ranitidine in the short-term treatment of duodenal ulcer: an Italian multicenter study. *Hepato-Gastroenterology* 34: 229-232, 1987
- Bardhan KD. Intermittent treatment of duodenal ulcer for long term medical management. *Postgraduate Medical Journal* 64 (Suppl. 1): 40-46, 1988
- Bardhan KD, Bianchi Porro G, Bose K, Daly M. A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. *Journal of Clinical Gastroenterology* 8: 408-413, 1986
- Bardhan KD, Dhande D, Hinchliffe RFC, Morris P, Thompson M, et al. Treatment of ultra refractory duodenal ulcer with omeprazole. *Abstract. Gut* 29: A724, 1988
- Bardhan KD, Morris P, Thompson M, Dhande DS, Hinchliffe RFC, et al. Omeprazole in the treatment of erosive oesophagitis refractory to high dose cimetidine and ranitidine. *Gut* 31: 745-749, 1990
- Bardhan KD, Naesdal J, Bianchi Porro G, Petrillo M, Lazzaroni M, et al. Treatment of refractory peptic ulcer with omeprazole or continued H<sub>2</sub> receptor antagonists: a controlled clinical trial. *Gut* 32: 435-438, 1991
- Bardram L, Thomsen P, Stadil F. Gastric endocrine cells in omeprazole-treated and untreated patients with the Zollinger-Ellison syndrome. *Digestion* 35 (Suppl. 1): 116-122, 1986
- Bardram L, Stadil F. Omeprazole in the Zollinger-Ellison syndrome. *Scandinavian Journal of Gastroenterology* 21: 371-378, 1986
- Bardram L, Stadil F. Effects of omeprazole on acid secretion and acid-related symptoms in patients with Zollinger-Ellison syndrome. *Scandinavian Journal of Gastroenterology* 24 (Suppl. 166): 95-100, 1989
- Bate CM. Omeprazole vs ranitidine. *Correspondence. Gut* 30: 1437, 1989
- Bate CM, Keeling PWN, O'Morain CA, Wilkinson SP, Mountford RA, et al. Omeprazole provides faster healing and symptom relief of reflux oesophagitis than cimetidine. *Abstract. Gut* 30: A1493, 1989a
- Bate CM, Wilkinson SP, Brady GVH, Bateson MC, Hislop WS, et al. Randomised, double-blind comparison of omeprazole and cimetidine in the treatment of symptomatic gastric ulcer. *Gut* 30: 1323-1328, 1989b
- Beil W, Staar U, Schünemann P, Sewing K-Fr, et al. Omeprazole, SCH 28080 and doxepin differ in their characteristics to inhibit H<sup>+</sup>/K<sup>+</sup>-ATPase driven proton accumulation by parietal cell membrane vesicles. *Biochemical Pharmacology* 37: 4487-4493, 1988
- Belgian Multicentre Group. Rate of duodenal ulcer healing during treatment with omeprazole. A double-blind comparison of a daily dose of 30mg versus 60mg. *Scandinavian Journal of Gastroenterology* 21 (Suppl. 118): 175-176, 1986
- Bendtsen F, Rune SJ. Intraduodenal pH during omeprazole treatment in duodenal ulcer patients. *Scandinavian Journal of Gastroenterology* 21 (Suppl. 118): 156-157, 1986
- Berlin RG. Omeprazole. Gastrin and gastric endocrine cell data from clinical studies. *Digestive Diseases and Sciences* 36: 129-136, 1991
- Betton GR, Dormer CS, Wells T, Pert P, Price CA, et al. Gastric ECL-Cell hyperplasia and carcinoids in rodents following chronic administration of H<sub>2</sub>-antagonists SK&F 93479 and omeprazole. *Toxicologic Pathology* 16: 288-298, 1988
- Bianchi Porro G, Bolling E, Barbara L, Blasi A, Capurso L, et al. Maintenance treatment with omeprazole in the prevention of duodenal ulcer relapse: a double-blind comparative trial. *Abstract. Gastroenterology* 98 (Suppl. 5): A21, 1990b
- Bianchi Porro G, Parente F. Duodenal ulcers resistant to H<sub>2</sub> blockers: An emerging therapeutic problem. *Scandinavian Journal of Gastroenterology* 23 (Suppl. 153): 81-87, 1988
- Bianchi Porro G, Santalucia F, Petrillo M. Omeprazole v sucralfate in the treatment of NSAID-induced gastric and duodenal ulcer. *Abstract. Gut* 31: A1175, 1990a
- Biasco G, Miglioli M, Barbara L, Corinaldesi R, Di Febo G, et al. Omeprazole, helicobacter pylori, gastritis, and duodenal ulcer. *Abstract. Lancet* 2: 1403, 1989
- Bigard MA. Prevention of aspirin-induced gastric lesions by ome-

- prazole in healthy subjects. *Scandinavian Journal of Gastroenterology* 24 (Suppl. 166): 182, 1989
- Bigard MA, Isal JP. Complete prevention by omeprazole of aspirin-induced gastric lesions in healthy subjects. *Gut* 29: A712, 1988
- Bigard MA, Isal JP, Galmiche JP, Ebrard F, Bader JP, et al. Omeprazole versus cimetidine in short-term treatment of acute duodenal ulcer. *Gastroentérologie Clinique et Biologique* 11: 753-757, 1987
- 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. An open multicentric trial of omeprazole in short-term treatment of duodenal ulcer. *Gastroentérologie Clinique et Biologique* 8: 943-946, 1984
- Blom H. Alterations in gastric mucosal morphology induced by long-term treatment with omeprazole in rats. *Digestion* 35 (Suppl. 1): 98-105, 1986
- Blum AL. Treatment of acid-related disorders with gastric acid inhibitors: the state of the art. *Digestion* 47 (Suppl. 1): 3-10, 1990
- Bonfils S, Mignon M. Management of Zollinger-Ellison syndrome with gastric antisecretory drugs. *Scandinavian Journal of Gastroenterology* 23 (Suppl. 146): 111-120, 1988
- Böttcher G, Häkanson R, Nilsson G, Seensalu R, Sundler F. Effects of long-term hypergastrinaemia on the ultrastructure of enterochromaffin-like cells in the stomach of the rat, hamster and guinea pig. *Cell and Tissue Research* 256: 247-257, 1989
- Brogden RN, Carmine AA, Heel RC, Speight TM, Avery GS, et al. Ranitidine: a review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. *Drugs* 24: 267-303, 1982
- Brunner G, Creutzfeldt W. Omeprazole in the long-term management of patients with acid-related diseases resistant to ranitidine. *Scandinavian Journal of Gastroenterology* 24 (Suppl. 166): 101-105, 1989
- Brunner GHG, Lamberts R, Creutzfeldt W. Efficacy and safety of omeprazole in the long-term treatment of peptic ulcer and reflux oesophagitis resistant to ranitidine. *Digestion* 47 (Suppl. 1): 64-68, 1990
- Burinson B. An *in vivo* unscheduled DNA synthesis (UDS) assay in the rat gastric mucosa: preliminary development. *Carcinogenesis* 10: 1425-1428, 1989
- Cadranel JF, Ruszniewski P, Elovaer-Blanc L, Leh T, Delchier JC, et al. Long term efficacy and tolerability of omeprazole in 20 patients presenting with severe Zollinger-Ellison syndrome. *Gastroentérologie Clinique et Biologique* 13: 654-662, 1989
- Carlsson E. A review of the effects of long-term acid inhibition in animals. *Scandinavian Journal of Gastroenterology* 24 (Suppl. 166): 19-23, 1989
- Carlsson E, Havu N, Mattsson H, Ekman L. Gastrin and gastric enterochromaffin-like cell carcinoids in the rat. *Digestion* 47 (Suppl. 1): 17-23, 1990
- Carlsson E, Larsson H, Mattsson H, Ryberg B, Sundell G. Pharmacology and toxicology of omeprazole - with special reference to the effects on the gastric mucosa. *Scandinavian Journal of Gastroenterology* 21: 31-38, 1986
- Cederberg C, Andersson T, Skånberg I. Omeprazole: pharmacokinetics and metabolism in man. *Scandinavian Journal of Gastroenterology* 24 (Suppl. 166): 33-40, 1989
- Ching MS, Mihaly GW, Angus PW, Morgan DJ, Devenish-Meares S, et al. Oral bioavailability of omeprazole before and after chronic therapy in patients with duodenal ulcer. *British Journal of Clinical Pharmacology* 31: 166-170, 1991
- Ching MS, Morgan DJ, Mihaly GW, Hardy KJ, Smallwood RA. Placental transfer of omeprazole in maternal and fetal sheep. *Developmental Pharmacology and Therapeutics* 9: 323-331, 1986
- Classen M, Dammann HG, Domschke W, Hüttemann E, Lohdeng W, et al. Healing rate of gastric ulcer after treatment with omeprazole or ranitidine: results of a German multicentre trial. *Deutsche Medizinische Wochenschrift* 110: 628-633, 1985
- Clissold SP, Campoli-Richards DM. Omeprazole: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. *Drugs* 32: 15-47, 1986
- Cooperative Study Group. Omeprazole in duodenal ulceration: acid inhibition, symptom relief, endoscopic healing, and recurrence. *British Medical Journal* 289: 525, 1984
- Cooperative Study Group. Double blind comparative study of omeprazole and ranitidine in patients with duodenal or gastric ulcer: a multicentre trial. *Gut* 31: 653-656, 1990
- Creutzfeldt W, Lamberts R. Is hypergastrinaemia dangerous to man? *Scandinavian Journal of Gastroenterology* 26 (Suppl. 180): 179-191, 1991
- Creutzfeldt W, Lamberts R, Stöckmann F, Brunner G. Quantitative studies of gastric endocrine cells in patients receiving long-term treatment with omeprazole. *Scandinavian Journal of Gastroenterology* 24 (Suppl. 166): 122-128, 1989
- Creutzfeldt W, Stöckmann F, Conlon JM, Fölsch UR, Bonatz G, et al. Effect of short- and long-term feeding of omeprazole in rat gastric endocrine cells. *Digestion* 35 (Suppl. 1): 84-97, 1986
- Crowe JP, Wilkinson SP, Bate CM, Willoughby CP, Peers EM, et al. Symptom relief and duodenal ulcer healing with omeprazole or cimetidine. *Alimentary Pharmacology and Therapeutics* 3: 83-91, 1989
- Dahlgren S, Domellöf L, Hradsky M, Norryd C, Brunkwall J, et al. The effects of omeprazole and cimetidine on duodenal ulcer healing and the relief of symptoms. *Alimentary Pharmacology and Therapeutics* 2: 483-492, 1988
- D'Adda T, Pilato FP, Lazzaroni M, Robutti F, Bianchi-Porro G, et al. Ultrastructural morphometry of gastric endocrine cells before and after omeprazole. A study in the oxyntic mucosa of duodenal ulcer patients. *Gastroenterology*, in press, 1991
- Daneshmend TK, Stein AG, Bhaskar NK, Hawkey CJ. Abolition by omeprazole of aspirin-induced gastric mucosal injury in humans. Abstract. *Gut* 29: A1442, 1988
- Danish Omeprazole Study Group. Relapse of gastric ulcers after treatment with omeprazole and cimetidine. A double-blind follow-up study. *Scandinavian Journal of Gastroenterology* 24: 557-560, 1989
- Daw MA, Deegan P, Beattie S, Leen E, Keane CT, et al. Suppression of *Helicobacter pylori* during the clinical use of omeprazole. Abstract. *Gut* 31: A1199, 1990
- de Bruyne JW, Klinkenberg-Knol EC, Jansen JBMJ, Lamers GF, Nelis HPM, et al. Long-term efficacy and safety of omeprazole (OME) on healing and prevention of resistant reflux esophagitis. Abstract. *Netherlands Journal of Medicine* 37 (Suppl. 2): A72, 1990
- Dehn TCB, Shepherd HA, Colin-Jones D, Kettlewell MGW, Carroll NGH. Double blind comparison of omeprazole (40mg od) versus cimetidine (400mg qd) in the treatment of symptomatic erosive reflux oesophagitis, assessed endoscopically, histologically and by 24h pH monitoring. *Gut* 31: 509-513, 1990
- Delchier J-C, Isal J-P, Eriksson S, Soule J-C. Double-blind multicentre comparison of omeprazole 20mg once daily versus ranitidine 150mg twice daily in the treatment of cimetidine or ranitidine resistant duodenal ulcers. *Gut* 30: 1173-1178, 1989
- Delchier J-C, Soule J-C, Mignon M, Goldfain D, Cartot A, et al. Effectiveness of omeprazole in seven patients with Zollinger-Ellison syndrome resistant to histamine H<sub>2</sub>-receptor antagonists. *Digestive Diseases and Sciences* 31: 693-699, 1986
- Delle Fave G, Annibale B, Helander H, Puoti M, Corleto V, et al.

- al. Omeprazole versus high dose ranitidine in H<sub>2</sub>-blocker-resistant duodenal ulcer patients. European Journal of Gastroenterology and Hepatology 3: 337-342, 1991
- Dent J. Australian clinical trials of omeprazole in the management of reflux oesophagitis. Digestion 47 (Suppl. 1): 69-71, 1990
- Dent J, Klinkenberg-Knol EC, Elm G, Eriksson K, Rikner L, et al. Omeprazole in the long-term management of patients with reflux oesophagitis refractory to histamine H<sub>2</sub>-receptor antagonists. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 176, 1989
- Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C, et al. Toxicological studies on omeprazole. Scandinavian Journal of Gastroenterology 20 (Suppl. 108): 53-69, 1985
- Elander B, Fellenius E, Leth R, Olbe L, Wallmark B. Inhibitory action of omeprazole on acid formation in gastric glands and on H<sup>+</sup>, K<sup>+</sup>-ATPase isolated from human gastric mucosa. Scandinavian Journal of Gastroenterology 21: 268-272, 1986
- England S, Daly MJ, Jacob S, Bardhan KD. Comparison of the inhibitory characteristics of cimetidine and omeprazole on human isolated parietal cells. Abstract. British Journal of Clinical Pharmacology 29: 610P, 1990
- Evans HJ. Tests for genotoxicity: principles and findings in relation to omeprazole. Digestion 47 (Suppl. 1): 45-48, 1990
- Farup PG, Darle N, Falk A, Bernklev T. Treatment of benign gastric ulcer with omeprazole 30mg once daily. Current Therapeutic Research 43: 872-877, 1988
- Farup PG, Rosseland AR, Halvorsen L, Andersen OK, Bernklev T. Duodenal ulcer treated with omeprazole: healing and relapse rates. Does treatment duration influence subsequent remission? Scandinavian Journal of Gastroenterology 24: 1107-1112, 1989
- Festen H, Tuynman H, Hollander W, Meuwissen S. Repeated high oral doses of omeprazole do not affect intrinsic factor secretion: proof of a selective mode of action. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 155, 1989
- Figala V, Klemm K, Kohl B, Kruger U, Rainer G, et al. Acid activation of H<sup>+</sup> + K<sup>+</sup>-ATPase inhibiting 2-(2-pyridyl-methyl-sulfanyl)-benzimidazoles: isolation and characterization of the thiophilic 'active principle' and its reactions. Journal of the Chemical Society. Chemical Communications pp. 125-127, 1986
- Forsell H, Helander HF, Sundell GW. Structure and function of the dog gastric mucosa during and after a 1-year treatment with omeprazole. I. Macro- and microscopic findings. Scandinavian Journal of Gastroenterology 21 (Suppl. 18): 79-80, 1986
- Francavilla A, Ingrosso M, Mongelli A, Baldassarre M, Giaccari S, et al. Omeprazole: a new antisecretory drug in the treatment of gastric ulcer. Abstract. Digestive Diseases and Sciences 31 (Suppl.): 335S, 1986
- French Cooperative Study. Omeprazole versus ranitidine in duodenal ulcer patients unhealed after six weeks treatment with H<sub>2</sub>-receptor antagonists. Abstract. Gut 28: A1341, 1987
- Fryklund J, Gedda K, Wallmark B. Specific labelling of gastric H<sup>+</sup>, K<sup>+</sup>-ATPase by omeprazole. Biochemical Pharmacology 37: 2543-2549, 1988b
- Fryklund J, Helander HF, Elander B, Wallmark B. Function and structure of parietal cells after H<sup>+</sup>-K<sup>+</sup>-ATPase blockade. American Journal of Physiology 254: G399-G407, 1988a
- Glise H, Martinson J, Solhaug JH, Carling L, Unge P, et al. The Scandinavian Clinics for United Research. Two and four weeks' treatment for duodenal ulcer. Symptom relief and clinical remission comparing omeprazole and ranitidine. Scandinavian Journal of Gastroenterology 26: 137-145, 1991
- Gloria VI, Domingo EO, Makalinao AU, Zaño FM, Rasco ET, et al. A comparison of omeprazole and ranitidine in the management of patients with duodenal ulcer. European Journal of Gastroenterology and Hepatology 3: 215-221, 1991
- Goldfain D, LeBodic MF, Lavergne A, Galian A, Modigliani R. Gastric carcinoid tumours in patients with Zollinger-Ellison syndrome on long-term omeprazole. Lancet 1: 776-777, 1989
- Graham DY, McCullough A, Sklar M, Sontag SJ, Roufaill WM, et al. Omeprazole versus placebo in duodenal ulcer healing. The United States experience. Digestive Diseases and Sciences 35: 66-72, 1990
- Graham DY, Van Deventer G, Humphries TJ, Cagliola RS, Berman K, et al. The natural history of duodenal ulcer (DU) disease is unchanged following treatment with omeprazole (OME), ranitidine (RAN) or placebo (PBO). Abstract. American Journal of Gastroenterology 84: 1184, 1989
- Grant SM, Langtry HD, Brogden RN. Ranitidine: an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in peptic ulcer disease and other allied diseases. Drugs 37: 801-870, 1989
- Guerreiro AS, Neves BC, Quina MG. Omeprazole in the treatment of peptic ulcers resistant to H<sub>2</sub>-receptor antagonists. Alimentary Pharmacology and Therapeutics 4: 309-313, 1990
- Gugler R, Jensen JC. Omeprazole inhibits elimination of diazepam. Correspondence. Lancet 1: 969, 1984
- Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism. Studies with diazepam and phenytoin *in vivo* and 7-ethoxycoumarin *in vitro*. Gastroenterology 89: 1235-1241, 1985
- Gugler R, Jensen JC. Drugs other than H<sub>2</sub>-receptor antagonists as clinically important inhibitors of drug metabolism *in vivo*. Pharmacology and Therapeutics 33: 133-137, 1987
- Guslandi M, Franceschi M, Pellegrini A, Tittobello A. Effects of omeprazole treatment on gastric mucus in man. Abstract. Gastroenterology 98 (Suppl. 5): A54, 1990
- Gustavsson S, Nyren O, Adamil H-O, Forhaug K, Knutsson L, et al. Omeprazole heals duodenal and prepyloric ulcers faster than cimetidine - a single-centre trial. Abstract. Gastroenterology 92: 1420, 1987
- Harvard Davis R, Stott NCH, Barber JH, Freeling P, Peers EM, et al. Treatment of peptic ulcer in general practice and in hospital: a comparison of omeprazole and cimetidine. British Journal of Clinical Practice 44: 13-16, 1990
- Havelund T, Laursen LS, Skoubo-Kristensen E, Andersen BN, Pedersen SA, et al. Omeprazole and ranitidine in treatment of reflux oesophagitis: double blind comparative trial. British Medical Journal 296: 89, 1988
- Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after lifelong inhibition of gastric secretion. Digestion 35 (Suppl. 1): 42-55, 1986
- Havu N, Maaroos MI, Siiponen P. The association between chronic atrophic gastritis and focal hyperplasia of argyrophil cells in gastric ulcer patients. Scandinavian Journal of Gastroenterology 26 (Suppl. 183): F31, 1991
- Havu N, Mattsson H, Ekman L, Carlsson E. Enterochromaffin-cell carcinoids in the rat gastric mucosa following long-term administration of ranitidine. Digestion 45: 189-195, 1990
- Helander HF. Oxytic mucosa histology in omeprazole-treated patients suffering from duodenal ulcer or Zollinger-Ellison syndrome. Digestion 35 (Suppl. 1): 123-129, 1986
- Helander HF, Larsson H, Carlsson E. Correspondence. Lancet 335: 910-911, 1990a
- Helander HF, Simonsson M, Sundler F, Rutgersson K, Helander KG, et al. Histology of gastric biopsies from peptic ulcer patients before and after short-term treatment with omeprazole or H<sub>2</sub>-receptor antagonists. Virchows Archiv A Pathological Anatomy and Histopathology 417: 305-309, 1990b
- Henry D, Brent P, Whyte I, Mihaly G, Devenish-Mearns S. Propranolol steady-state pharmacokinetics are unaltered by ome-

- prazole. European Journal of Clinical Pharmacology 33: 369-373, 1987
- Hetzel DJ, Dent J, Reed WD, Narielvala FM, MacKinnon M. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 95: 903-912, 1988
- Hetzel DJ, Korman MG, Hansky J, Eaves ER, Shearman DJC, et al. A double blind multicentre comparison of omeprazole and cimetidine in the treatment of duodenal ulcer. Abstract. Australian and New Zealand Journal of Medicine 16 (Suppl. 3): 595, 1986
- Hirschowitz BI, Deren J, Raufman JP, Lamont B, Berman R, et al. A multicenter US study of omeprazole treatment of Zollinger-Ellison syndrome (ZES). Abstract. Gastroenterology 94 (Pt 2): A188, 1988
- Hirschowitz B, Holt S, Robinson M, Behar J, Sontag S, et al. Omeprazole (OME) is superior to placebo (PBO) in the complete relief of heartburn and endoscopic healing in patients with reflux esophagitis (RE): US multicenter dose ranging study results. Abstract. American Journal of Gastroenterology 84: 1144, 1989
- Holt S, Zhu Z, Grady T, Powers R. Is omeprazole genotoxic? American Journal of Gastroenterology 85: 1291, 1990
- Howden CW, Beastall GH, Reid JL. An investigation into the effects of omeprazole on renal tubular function and endocrine function in man. Scandinavian Journal of Gastroenterology 21 (Suppl. 118): 169-170, 1986a
- Howden CW, Derodra JK, Burget DW, Hunt RH. Effects of low dose omeprazole on gastric secretion and plasma gastrin in patients with healed duodenal ulcer. Hepato-Gastroenterology 33: 267-270, 1986b
- Howden CW, Kenyon CJ, Beastall GH, Reid JL. Inhibition by omeprazole of adrenocortical response to ACTH: clinical studies and experiments on bovine adrenal cortex *in vitro*. Clinical Science 70: 99-102, 1986c
- Howden CW, Meredith PA, Forrest JAH, Reid JL. Oral pharmacokinetics of omeprazole. European Journal of Clinical Pharmacology 26: 641-643, 1984a
- 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, 1984b
- Howden CW, Reid JL. The effect of antacids and metoclopramide on omeprazole absorption and disposition. Letter. British Journal of Clinical Pharmacology 25: 779-780, 1988
- Hui WM, Chen BW, Cho CH, Lam SK, Luk CT. The effect of misoprostol, omeprazole and sucralfate on nicotine- and ethanol-induced gastric injury and gastric mucosal blood flow: A comparative study. Journal of Gastroenterology and Hepatology 5: 653-658, 1990
- Hui WM, Lam SK, Lau WY, Branick FJ, Lai CL, et al. Omeprazole (OME) v ranitidine (RAN) for duodenal ulcer - weekly endoscopic assessment. Abstract. Gut 28: A1340, 1987
- Humphries TJ, Ekkenved 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
- Håkanson R, Axelson J, Ekman R, Sundler F. Hypergastrinaemia evoked by omeprazole stimulates growth of gastric mucosa but not of pancreas or intestines in hamster, guinea pig and chicken. Regulatory Peptides 23: 105-115, 1988
- Hüttemann W. Short-term treatment of gastric ulcer with once daily omeprazole. Scandinavian Journal of Gastroenterology 21 (Suppl. 18): 179, 1986
- Hüttemann W, Rohner 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
- Jansen JBMJ, Klinkenberg-Knol EC, Meuwissen SGM, Bruijne JW, Festen HPM, et al. Effect of long-term treatment with omeprazole on serum gastrin and serum group A and C peptides in patients with reflux esophagitis. Gastroenterology 99: 621-628, 1990
- Jensen JC, Gugler R. Inhibition of human liver cytochrome P-450 by omeprazole. British Journal of Clinical Pharmacology 21: 328-330, 1986
- Jensen RT, Maton PN, Gardner JD. Current management of Zollinger-Ellison syndrome. Drugs 32: 188-196, 1986
- Karvonen A-L, Keyriläinen O, Uusitalo A, Salaspuro M, Tarpila S, et al. Effects of omeprazole in duodenal ulcer patients. Scandinavian Journal of Gastroenterology 21: 419-454, 1986
- Kittang E, Aadland E, Schjensby H. Effect of omeprazole on the secretion of intrinsic factor, gastric acid and pepsin in man. Gut 26: 594-598, 1985
- Klinkenberg-Knol EC, Festen HPM, Meuwissen SGM. The effects of omeprazole and ranitidine on 24-hour pH in the distal oesophagus of patients with reflux oesophagitis. Alimentary Pharmacology and Therapeutics 2: 221-227, 1988a
- Klinkenberg-Knol EC, Jansen JBMJ, de Bruyne JW, Nelis GF, Festen HPM, et al. Longterm efficacy and safety of omeprazole (OME) on healing and prevention of resistant reflux esophagitis. Abstract. Gastroenterology 9 (Pt 2): A230, 1988b
- Klinkenberg-Knol EC, Jansen JBMJ, Festen HPM, Meuwissen SGM, Lamers CBHW. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. Lancet 1: 349-350, 1987
- Klinkenberg-Knol EC, Jansen JBMJ, Lamers CBHW, Nelis F, Meuwissen SGM. Temporary cessation of long-term maintenance treatment with omeprazole in patients with H<sub>2</sub>-receptor-antagonist-resistant reflux oesophagitis. Effects on symptoms, endoscopy, serum gastrin, and gastric acid output. Scandinavian Journal of Gastroenterology 25: 1144-1150, 1990
- Koop H, Hotz J, Pommer G, Klein M, Arnold R. Prospective evaluation of omeprazole treatment in reflux oesophagitis refractory to H<sub>2</sub>-receptor antagonists. Alimentary Pharmacology and Therapeutics 4: 593-599, 1990a
- Koop H, Klein M, Arnold R. Serum gastrin levels during long-term omeprazole treatment. Alimentary Pharmacology and Therapeutics 4: 131-138, 1990b
- Koop H, Schwarting H, Knorr-Marin A, Willhardt C, Möser T, et al. Influence of chronic omeprazole treatment on gastric endocrine function. Klinische Wochenschrift 65: 169-173, 1987
- Lamberts R, Creutzfeldt W, Stöckmann F, Jacobaschke V, Maas S, et al. Long-term omeprazole treatment in man: effects on gastric endocrine cell populations. Digestion 39: 126-135, 1988
- Lamers CBHW. Hormonal regulation of gastric acid in peptic ulcer disease. Scandinavian Journal of Gastroenterology 23 (Suppl. 146): 5-10, 1988
- 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. Abstract. Gut 26: A1134-A1135, 1985
- Langman JS. Antisecretory drugs and gastric cancer. British Medical Journal 290: 1850-1852, 1985
- Lanza F, Simon TJ, Berlin RG, Berman R, Keyser J, et al. Is 20mg the appropriate daily dosage of omeprazole (Ome) for healing active duodenal ulcer in the U.S. target population? Gastroenterology 100: A167, 1991
- Lanzon-Miller S, Pounder RE, Hamilton MR, Ball S, Chronos NAF, et al. Twenty-four-hour intragastric acidity and plasma

- gastrin concentration before and during treatment with either ranitidine or omeprazole. *Alimentary Pharmacology and Therapeutics* 1: 239-251, 1987a
- Lanzon-Miller S, Pounder RE, Hamilton MR, Chronos NAF, Ball S, et al. Twenty-four-hour intragastric acidity and plasma gastrin concentration in healthy subjects and patients with duodenal or gastric ulcer, or pernicious anaemia. *Alimentary Pharmacology and Therapeutics* 1: 225-237, 1987
- Larson GM, Sullivan HW, Rayford P. Omeprazole-induced hypergastrinemia: role of gastric acidity. *Journal of Surgical Research* 40: 504-509, 1986
- Larsson H, Carlsson E, Häkanson R, Mattsson H, Nilsson G, et al. Time-course of development and reversal of gastric endocrine cell hyperplasia after inhibition of acid secretion. Studies with omeprazole and ranitidine in intact and antrectomized rats. *Gastroenterology* 95: 1477-1486, 1988a
- Larsson H, Fryklund J, Helander HF, Wallmark B. Partial proteinase digestion of rat gastric mucosa isolates cells undergoing replicative DNA synthesis. *Mutagenesis* 6: 3-9, 1991
- Larsson H, Häkanson R, Mattsson H, Ryberg B, Sundler F, et al. Omeprazole: its influence on gastric acid secretion, gastrin and ECL cells. *Toxicologic Pathology* 16: 267-272, 1988b
- Larsson H, Mattsson H, Sundell G, Carlsson E. Animal pharmacodynamics of omeprazole. A survey of its pharmacological properties *in vivo*. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 23-35, 1985
- Lauritsen K, Andersen BN, Havelund T, Laursen LS, Hansen J, et al. Effect of 10 mg and 20 mg omeprazole daily on duodenal ulcer: double-blind comparative trial. *Alimentary Pharmacology and Therapeutics* 3: 59-67, 1989a
- Lauritsen K, Andersen BN, Laursen LS, et al. Weekend administration of omeprazole in the prevention of duodenal ulcer relapse: A double-blind comparative trial. *Gastroenterology* 96: A289, 1989b
- Lauritsen K, Andersen BN, Laursen LS, Hansen J, Havelund T, et al. Omeprazole 20 mg three days a week and 10 mg daily in prevention of duodenal ulcer relapse. Double-blind comparative trial. *Gastroenterology* 100: 663-669, 1991
- Lauritsen K, Rune SJ, Bytzer P, Kelbaek H, Gotlieb Jensen K, et al. Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. *New England Journal of Medicine* 312: 958-961, 1985
- Lauritsen K, Rune SJ, Wulff HR, Olsen JH, Laursen LS, et al. Effect of omeprazole and cimetidine on prepyloric gastric ulcer: double blind comparative trial. *Gut* 29: 249-253, 1988
- Lee M-L, Piper DW, Fischer GO, De Launey WE. Lichen spinulosus after the ingestion of omeprazole. Correspondence. *Medical Journal of Australia* 150: 410, 1989
- Lehy T, Mignon M, Cadiot G, Elouera-Blanc L, Ruszniewski Ph, et al. Gastric endocrine cell behavior in Zollinger-Ellison patients upon long-term potent antisecretory treatment. *Gastroenterology* 96: 1029-1040, 1989
- Li G, Klotz Y. Inhibitory effect of omeprazole on the metabolism of midazolam in vitro. *Arzneimittel-Forschung* 40: 1105-1107, 1990
- Lind T, Andersson T, Skanberg I, Olbe L. Biliary excretion of intravenous [<sup>14</sup>C] omeprazole in humans. *Clinical Pharmacology and Therapeutics* 42: 504-508, 1987
- Lind T, Cederberg C, Forssell H, Olausson M, Olbe L. Relationship between reduction of gastric acid secretion and plasma gastrin concentration during omeprazole treatment. *Scandinavian Journal of Gastroenterology* 23: 1259-1266, 1988
- Lind T, Cederberg C, Idström JP, Olausson M, Lonroth H. 24-hour intragastric acidity and plasma gastrin during short and long-term treatment with omeprazole or ranitidine. *Gastroenterology* 5: A79, 1990b
- Lind T, Cederberg C, Olausson M, Olbe L. 24-hour intragastric acidity and plasma gastrin after omeprazole treatment and after proximal gastric vagotomy in duodenal ulcer patients. *Gastroenterology* 99: 1593-1598, 1990a
- Lind T, Moore M, Olbe L. Intravenous omeprazole: effect on 24-hour intragastric pH in duodenal ulcer patients. *Digestion* 34: 78-86, 1986
- Lindberg P, Brändström A, Wallmark B, Mattsson H, Rikner L, et al. Omeprazole: the first proton pump inhibitor. *Medical Research Review* 10: 1-54, 1990
- Lindberg P, Nordberg P, Alminger T, Brändström A, Wallmark B. The mechanism of action of the gastric acid secretion inhibitor omeprazole. *Journal of Medicinal Chemistry* 29: 1327-1329, 1986
- Lloyd-Davies KA, Rutgersson K, Sölvell L. Omeprazole in the treatment of Zollinger-Ellison syndrome: a 4-year international study. *Alimentary Pharmacology and Therapeutics* 2: 13-32, 1988
- London W, London D, Cederberg C, Steffen H. Dose-response study of omeprazole on meal-stimulated gastric acid secretion and gastrin release. *Gastroenterology* 85: 1373-1378, 1983
- Lorentzon P, Jackson R, Wallmark B, Sachs G. Inhibition of ( $H^+$ + $K^+$ )-ATPase by omeprazole in isolated gastric vesicles requires proton transport. *Biochimica et Biophysica Acta* 897: 41-51, 1987
- Lundell L, Backman L, Ekström P, Enander L-K, Falkmer S, et al. Prevention of relapse of reflux esophagitis after endoscopic healing: the efficacy and safety of omeprazole compared with ranitidine. *Scandinavian Journal of Gastroenterology* 26: 248-256, 1991
- Lundell L, Backman L, Ekström P, Enander L-H, Fausa O, et al. Omeprazole or high-dose ranitidine in the treatment of patients with reflux oesophagitis not responding to 'standard doses' of  $H_2$ -receptor antagonists. *Alimentary Pharmacology and Therapeutics* 4: 145-155, 1990
- Maaroos HI, Salupere V, Uibo R, Kekki M, Sipponen P. Seven-year follow-up study of chronic gastritis in gastric ulcer patients. *Scandinavian Journal of Gastroenterology* 20: 198-204, 1985
- MacGilchrist AJ, Howden CW, Kenyon CJ, Beastall GH, Reid JL. The effects of omeprazole on endocrine function in man. *European Journal of Clinical Pharmacology* 32: 423-425, 1987
- Mainguet HP, Helme M, Debongnie J-C. Omeprazole, *Campylobacter pylori*, and duodenal ulcer. *Lancet* 389: 389-390, 1989
- Man WK, Thompson JN, Baron JH, Spencer J. Histamine and duodenal ulcer: effect of omeprazole on gastric histamine in patients with duodenal ulcer. *Gut* 27: 418-422, 1986
- Marciano-D'Amore DA, Paterson WG, Da Costa LR, Beck IT. Omeprazole in  $H_2$  receptor antagonist-resistant reflux esophagitis. *Journal of Clinical Gastroenterology* 12: 616-620, 1990
- Marks DR, Joy JV, Bonheim NA. Hemolytic anemia associated with the use of omeprazole. *American Journal of Gastroenterology* 86: 217, 1991
- Marks IN, Winter TA, Lucke W, Wright JP, Newton KA, et al. Omeprazole and ranitidine in duodenal ulcer healing. *South African Medical Journal* 74 (Suppl.): 54-56, 1988
- Maton PN. Omeprazole. *New England Journal of Medicine* 324: 965-975, 1991
- Maton PN, Frucht H, Vinayek R, Wank SA, Gardner JD, et al. Medical management of patients with Zollinger-Ellison syndrome who have had previous gastric surgery: a prospective study. *Gastroenterology* 94: 294-299, 1988
- Maton PN, Lakck EE, Collen MJ, Cornelius MJ, David E, et al. The effect of Zollinger-Ellison syndrome and omeprazole therapy on gastric oxyntic endocrine cells. *Gastroenterology* 99: 943-950, 1990
- Maton PN, Vinayek R, Frucht H, McArthur KA, Miller LS, et al. Long-term efficacy and safety of omeprazole in patients with

- Zollinger-Ellison syndrome: a prospective study. *Gastroenterology* 97: 827-836, 1989
- Mattsson H. Protective effects of omeprazole in the gastric mucosa. *Scandinavian Journal of Gastroenterology* 21 (Suppl. 118): 86, 1986
- Mattsson H, Havu N, Bräutigam J, Carlsson K, Lundell L, et al. Partial gastric corpectomy results in hypergastrinemia and development of gastric enterochromaffinlike-cell carcinoids in the rat. *Gastroenterology* 100: 311-319, 1991
- McArthur KE, Collier MJ, Maton PN, Cherner JA, Howard JM, et al. Omeprazole: effective, convenient therapy for Zollinger-Ellison syndrome. *Gastroenterology* 88: 939-944, 1985
- McCarthy JH, Dent J, Hetzel DJ, Reed WD, Narielvala FM, et al. Omeprazole in the treatment of reflux oesophagitis. Abstract. *Australia and New Zealand Journal of Medicine* 16: 595, 1986
- McFarland RJ, Bateson MC, Green JRB, O'Donoghue DP, Dronfield MW, et al. Omeprazole provides quicker symptom relief and duodenal ulcer healing than ranitidine. *Gastroenterology* 98: 278, 1990
- McKee RF, MacGilchrist AJ, Garden OJ, Forrest JAH, Carter DC. The anti-secretory effect and pharmacokinetics of omeprazole in chronic liver disease. *Alimentary Pharmacology and Therapeutics* 2: 429-437, 1988
- McLauchlan G, Crean GP, McColl KEL. Effect of low-dose omeprazole on gastric acid secretion in duodenal ulcer patients. *Alimentary Pharmacology and Therapeutics* 2: 263-268, 1988
- Mignon M, Alcubes G, Lehy T, Nguyen Phuoc BK, Vatier J, et al. Modifications sécrétoires, pHmétriques, et ultrastructurales gastriques au cours d'un traitement prolongé par l'omeprazole dans une forme sévère de syndrome de Zollinger-Ellison. *Gastroenterologie Clinique et Biologique* 8: 947-954, 1984
- Mignon M, Lehy T, Bonnefond A, Ruszniewski P, Labeille D, et al. Development of gastric argyrophil carcinoid tumors in a case of Zollinger-Ellison syndrome with primary hyperparathyroidism during long-term antisecretory treatment. *Cancer* 59: 1959-1962, 1987
- Miller LS, Vinayek R, Frucht H, Gardner JD, Jensen RT, et al. Reflux esophagitis in patients with Zollinger-Ellison syndrome. *Gastroenterology* 98: 341-346, 1990
- Miyoshi A, et al. The effect of omeprazole and famotidine on duodenal ulcer - a double-blind comparative study. *Japanese Pharmacology and Therapeutics* 16 (Suppl. 3): 563, 1988a
- Miyoshi A, et al. The effect of omeprazole and famotidine on gastric ulcer - a double-blind comparative study. *Japanese Pharmacology and Therapeutics* 16 (Suppl. 3): 543, 1988b
- Miyoshi A, et al. A dose comparative study of omeprazole in gastric and duodenal ulcer disease. *Japanese Pharmacology and Therapeutics* 16 (Suppl. 3): 517, 1988c
- Morii M, Takata H, Fujisaki H, Takeguchi N. The potency of substituted benzimidazoles such as E3810, omeprazole, Ro 18-5364 to inhibit gastric H<sup>+</sup>,K<sup>+</sup>-ATPase is correlated with the rate of acid-activation of the inhibitor. *Biochemical Pharmacology* 39: 661-667, 1990a
- Morii M, Takata H, Takeguchi N. Acid activation of omeprazole in isolated gastric vesicles, oxyntic cells, and gastric glands. *Gastroenterology* 96: 1453-1461, 1989
- Morii M, Takata H, Takeguchi N. Binding site of omeprazole in hog gastric H<sup>+</sup>,K<sup>+</sup>-ATPase. *Biochemical and Biophysical Research Communications* 167: 754-760, 1990b
- Mulder CJJ, Schipper DL. Omeprazole and ranitidine in duodenal ulcer healing. Analysis of comparative clinical trials. *Scandinavian Journal of Gastroenterology* 25 (Suppl. 178): 62-66, 1990
- Mulder CJJ, Tytgat GNJ, Cluysenaer OJJ, Nicolai JJ, Meyer WW, et al. Omeprazole (20mg o.m.) versus ranitidine (150mg b.d.) in duodenal ulcer healing and pain relief. *Alimentary Pharmacology and Therapeutics* 3: 445-451, 1989
- Naesdal J, Andersson T, Bodemar G, Larsson R, Regårdh CG, et al. Pharmacokinetics of [<sup>14</sup>C]omeprazole in patients with impaired renal function. *Clinical Pharmacology and Therapeutics* 40: 344-351, 1986
- Naesdal J, Bankel M, Bodemar G, Gotthard R, Lundquist G, et al. The effect of 20 mg omeprazole daily on serum gastrin, 24-H intragastric acidity, and bile acid concentration in duodenal ulcer patients. *Scandinavian Journal of Gastroenterology* 22: 5-12, 1987
- Naesdal J, Lind T, Bergsåker-Aspöy J, et al. The rate of healing of duodenal ulcers during omeprazole treatment. *Scandinavian Journal of Gastroenterology* 20: 691-695, 1985
- Nelis GF. Safety profile of omeprazole. Adverse events with short-term treatment. *Digestion* 44 (Suppl. 1): 68-76, 1989
- Oddsson E, Gudjonsson H, Thjodleifsson B. Protective effect of omeprazole or ranitidine against naproxen induced damage to the human gastroduodenal mucosa. Abstract. *Scandinavian Journal of Gastroenterology* 25 (Suppl. 176): 25, 1990
- Pace F, Bianchi Porro G. Medical treatment of reflux oesophagitis: review of traditional therapies and omeprazole. *Italian Journal of Gastroenterology* 20 (Suppl.): 23-29, 1988
- Pen JH, Michielsen PP, Pelckmans PA, Van Maercke YM. Omeprazole in the treatment of H<sub>2</sub>-resistant gastroduodenal ulcers. Abstract. *Gastroenterology* 94 (Pt 2): A348, 1988
- Pilbrant A, Cederberg C. Development of an oral formulation of omeprazole. *Scandinavian Journal of Gastroenterology* 20 (Suppl. 108): 113-120, 1985
- Ponce J, Rodrigo JM. Therapeutic failure and relapse in peptic ulcer. *Methods and Findings in Experimental and Clinical Pharmacology* 11 (Suppl. 1): 123-130, 1989
- Pounder RE. Duodenal ulcers that will not heal. *Gut* 25: 697-702, 1984
- Poynter D. Omeprazole and genotoxicity. Correspondence. *Lancet* 335: 611, 1990
- Poynter D, Pick CR, Harcourt RA, Selway SAM, Ainge G, et al. Association of long lasting unsurmountable histamine H<sub>2</sub> 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, Walt RP, Kitchingman GK, Somerville KW, Langman MJS, et al. Oral phenytoin pharmacokinetics during omeprazole therapy. *British Journal of Clinical Pharmacology* 24: 543-545, 1987
- Prichard PJ, Yeomans ND, Mihaly GW, Jones DB, Buckle PJ, et al. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. *Gastroenterology* 88 (Pt 1): 64-69, 1985b
- Rasmussen L, Øster-Jørgensen E, Qvist N, Kraglund K, Hovendal C, et al. Short report: a double-blind placebo-controlled trial of omeprazole on characteristics of gastric emptying in healthy subjects. *Alimentary Pharmacology and Therapeutics* 5: 85-89, 1991
- Rauws EAJ, Langenberg W, Bosma A, Dankert J, Tytgat GNJ. Lack of eradication of *Helicobacter pylori* after omeprazole. *Lancet* 337: 1093, 1991
- Rauws EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GNJ. *Campylobacter pyloridis*-associated chronic active antral gastritis. A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. *Gastroenterology* 94: 33-40, 1988
- Regårdh CG. Pharmacokinetics and metabolism of omeprazole

- in man. Scandinavian Journal of Gastroenterology 21 (Suppl. 118): 99-104, 1986
- Regardh CG, Andersson T, Lagerström PO, Lundborg P, Skånberg I. The pharmacokinetics of omeprazole in humans - a study of single intravenous and oral doses. Therapeutic Drug Monitoring 12: 163-172, 1990
- Regardh CG, Gabrielsson M, Hoffman K-J, Löfberg I, Skånberg I. Pharmacokinetics and metabolism of omeprazole in animals and man - an overview. Scandinavian Journal of Gastroenterology 20 (Suppl. 108): 79-94, 1988
- Renberg L, Simonsson R, Hoffmann KJ. Identification of two main urinary metabolites of [<sup>14</sup>C]omeprazole in humans. Metabolism and Disposition 17: 69-76, 1989
- Rinetti M, Regazzi MB, Villani P, Tizzoni M, Sivelli R. Pharmacokinetics of omeprazole in cirrhotic patients. Arzneimittelforschung/Drug Research 41: 420, 1991
- Rinetti M, Vezzadini P, Jonsson E, Tomasetti P, Labo G. Effect and tolerability of omeprazole in the treatment of duodenal ulcer disease. Drugs in Experimental Clinical Research 12: 701-705, 1986
- Rogers M, Primrose JN, Carroll N, Daly MJ. Omeprazole but not cimetidine markedly inhibits pepsin secretion in patients with refractory duodenal ulcer. Abstract. Gut 31: A1200, 1990
- Roggio A, Filippini L, Colombi A. The effect of hemodialysis on omeprazole plasma concentrations in the anuric patient: a case report. International Journal of Clinical Pharmacology, Therapy and Toxicology 28: 115-117, 1990
- Röhner HG, Hüttemann W, du Bosque G, Rehner M, Hebbelin H, et al. Oral omeprazole, 20mg versus 30mg once daily: effect on healing rates in 115 duodenal ulcer patients. Scandinavian Journal of Gastroenterology 21: 173-174, 1986
- Romano M, Razandi M, Ivey KJ. Protection of gastric epithelial cell monolayers from a human cell line by omeprazole in vitro. Scandinavian Journal of Gastroenterology 24: 513-521, 1989
- Ruth M, Enbom H, Lundell L, Löroth H, Sandberg N, et al. Effect of omeprazole or ranitidine treatment on 24-hour oesophageal acidity in patients with reflux oesophagitis. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 173, 1989
- Ryberg B, Axelson J, Håkanson R, Sundler F, Mattsson H. Trophic effects of continuous infusion of [Leu<sup>15</sup>]-gastrin-17 in the rat. Gastroenterology 98: 33-38, 1990a
- Ryberg B, Bishop AE, Bloom SR, Carlsson E, Håkanson R, et al. Omeprazole and ranitidine, antisecretagogues with different modes of action, are equally effective in causing hyperplasia of enterochromaffin-like cells in rat stomach. Regulatory Peptides 25: 235-246, 1989
- Ryberg B, Carlsson E, Carlsson K, et al. Effects of partial resection of acid-secreting mucosa on plasma gastrin and enterochromaffin-like cells in the rat stomach. Digestion 45: 102-108, 1990
- Sabbatini F, Piai G, Mazzacca G. Italian multicentre studies with omeprazole in the treatment of peptic ulcer disease. Italian Journal of Gastroenterology 20 (Suppl.): 20-22, 1988
- Sachs G, Scott D, Reuben M. Omeprazole and the gastric mucosa. Digestion 47 (Suppl. 1): 35-38, 1990
- Sandmark S, Carlsson R, Fausa O, Lundell L. Omeprazole or ranitidine in the treatment of reflux esophagitis. Scandinavian Journal of Gastroenterology 23: 625-632, 1988
- Santucci L, Farroni F, Fiorucci S, Morelli A. Gynecomastia during omeprazole therapy. New England Journal of Medicine 324: 635, 1991
- Savarino V, Mela G, Sumberaz A, Celle G. Correspondence. Omeprazole in H<sub>2</sub> blocker non-responders. Gut 31: 584, 1990
- Scandinavian Multicentre Study. Gastric acid secretion and duodenal ulcer healing during treatment with omeprazole. Scandinavian Journal of Gastroenterology 19: 882-884, 1984
- Schiller KFR, Axon ATR, Carr-Locke DI, Cockel R, Donovan IA, et al. Duodenal ulcer recurrence after healing with omeprazole or cimetidine treatment: a multicentre study in the UK. Gut 30: A1490, 1989
- Scott D, Reuben M, Zampighi G, Sachs G. Cell isolation and genotoxicity assessment in gastric mucosa. Digestive Diseases and Sciences 35: 1217-1225, 1990
- Sellapah S. An unusual side effect of omeprazole: case report. British Journal of General Practice 40: 389, 1990
- Sharma BK, Walt RP, Pounder RE, Gomes MDeFA, Wood EC, et al. Optimal dose of oral omeprazole for maximal 24 hours decrease in intragastric acidity. Gut 25: 957-964, 1984
- Sharp J, Logan RPH, Walker MM, Gummelt PA, Misiewicz JJ, et al. Effect of omeprazole on *Helicobacter pylori*. Abstract. Gut 32: A565, 1991
- Simon B, Dammann HG, Müller P. Gastroduodenal tolerability of nonsteroidal antiinflammatory agents (NOSAC) in man: endoscopic comparative studies with antiulcer drugs. Abstract. Gastroenterology 90: 1635, 1986
- Skånberg I, Carlsson E, Karlsson A, Larsson H, Hofberg I, et al. The pharmacokinetics of omeprazole and correlation to inhibition of gastrin acid secretion. Acta Physiologica Scandinavica 124 (Suppl. 542): 266, 1985
- Solcia E, Bordi C, Creutzfeldt W, Dayal Y, Dayan AD, et al. Histopathological classification of nonantral gastric endocrine growths in man. Digestion 41: 185-200, 1988
- Solcia E, Rindi G, Havu N, Elm G. Qualitative studies of gastric endocrine cells in patients treated long-term with omeprazole. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 129-137, 1989
- Stern WR. Summary of the 34th meeting of the Food and Drug Administration Gastrointestinal Drugs Advisory Committee March 15 and 16, 1989. American Journal of Gastroenterology 84: 1351-1355, 1989
- Stöckmann F, Bernhard F, Möstar A, Nisslinger A, Creutzfeldt W. Morphological changes of gastric endocrine cells during treatment with omeprazole and famotidine. Abstract. Gastroenterology 94: A445, 1988
- Sundler F, Håkanson R, Carlsson E, Larsson H, Mattsson H, et al. Hypergastrinemia after blockade of acid secretion in the rat: trophic effects. Digestion 35 (Suppl. 1): 56-69, 1986
- Sutfin T, Balmer K, Boström H, Eriksson S, Höglund P, et al. Stereoselective interaction of omeprazole with warfarin in healthy men. Therapeutic Drug Monitoring 11: 176-184, 1989
- Sölvell L. The clinical safety of omeprazole. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 106-110, 1989
- Sölvell L. The clinical safety of omeprazole. Digestion 47 (Suppl. 1): 59-63, 1990
- Ten Kate RW, Tuynman HARE, Festen HPM, Pals G, Meuwissen SGM. Effect of high dose omeprazole on gastric pepsin secretion and serum pepsinogen levels in man. European Journal of Clinical Pharmacology 35: 173-176, 1988
- Tielemans Y, Håkanson R, Sundler F, Willems G. Proliferation of enterochromaffinlike cells in omeprazole-treated hypergastrinemic rats. Gastroenterology 96: 723-729, 1989
- Tuynman HARE, Festen HPM, Röhss K, Meuwissen SGM. Lack of effect of antacids on plasma concentrations of omeprazole given as enteric-coated granules. British Journal of Clinical Pharmacology 24: 833-835, 1987
- Tytgat GNJ, Lamers CBHW, Hameeteman W, Jansen JMBJ, Wilson JA. Omeprazole in peptic ulcers resistant to histamine H<sub>2</sub>-receptor antagonists. Alimentary Pharmacology and Therapeutics 1: 31-38, 1987
- Tytgat GNJ, Lamers CBHW, Wilson JA, Hameeteman W, Jansen JMBJ, et al. 100% healing with omeprazole of peptic ulcers resistant to histamine H<sub>2</sub>-receptor antagonists. Gastroenterology 88: 1620, 1985
- Tytgat GNJ, Nio CY, Schotborgh RH. Reflux esophagitis. Scan-

- dinavian Journal of Gastroenterology 25 (Suppl. 175): 1-12, 1990
- Tytgat GNJ, Nio CY. The medical therapy of reflux. *Balières Clinical Gastroenterology* 1: 791-807, 1987
- Unge P, Olsson J, Gad A, Gnarpe H. Does omeprazole, 40 mg o.m., improve antimicrobial therapy directed towards gastric *Camyllobacter pylori* in patients with antral gastritis? Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 184, 1989
- Valenzuela JE, Berlin RG, Snape WJ, Johnson TL, Hirschowitz BI, et al. U.S. experience with omeprazole in duodenal ulcer. Multicenter double-blind comparative study with ranitidine. *Digestive Diseases and Sciences* 36: 761-768, 1991
- Vantrappen G, Rutgeerts L, Schurmans P, Coenegrachts J-L. Omeprazole (40 mg) is superior to ranitidine in short-term treatment of ulcerative reflux esophagitis. *Digestive Diseases and Sciences* 33: 523-529, 1988
- 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
- Vinayek R, Frucht H, London JF, Miller LS, Stark HA, et al. Histological healing of peptic oesophagitis with omeprazole. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 174, 1989
- Vinayek R, Frucht H, London JF, Miller LS, Stark HA, et al. Intravenous omeprazole in patients with Zollinger-Ellison syndrome undergoing surgery. *Gastroenterology* 99: 10-16, 1990
- Walsh A, Bader J-P, Classen M, Lamers BHW, Piper DW, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *New England Journal of Medicine* 320: 69-75, 1989
- Wallmark B. Proton pump inhibitors - mechanism of action of omeprazole and its effect on gastric acid secretion. Canadian Journal of Gastroenterology 3 (Suppl. A): 37A-42A, 1989
- Wallmark B, Larsson H, Andersson K, Fryklund J, Helander HF. Tritiated thymidine incorporation into DNA in rat gastric mucosal cells. *Digestion* 47 (Suppl. 1): 39-44, 1990
- Wallmark B, Larsson M, Humble L. The relationship between gastric acid secretion and gastric H<sup>+</sup>, K<sup>+</sup>-ATPase activity. *Journal of Biological Chemistry* 260: 13681-13684, 1985
- Walsh JH. Role of gastrin as a trophic hormone. *Digestion* 47 (Suppl. 1): 11-16, 1990
- Whitehead R, Hetzel DJ, Dent J, Reed W, Narielvala F, et al. Histological healing of peptic oesophagitis with omeprazole. Scandinavian Journal of Gastroenterology 24 (Suppl. 166): 174, 1989
- Wong PYN, Lane MR. Omeprazole 20 mg daily for duodenal ulcer: a multicentre study. *New Zealand Medical Journal* 104: 140, 1991
- Wright NA. DNA synthesis and genotoxicity. *Digestion* 47 (Suppl. 1): 24-30, 1990
- Wright NA, Goodlad RA. Omeprazole and genotoxicity. Letter. *Lancet* 335: 909-910, 1990
- Zeitoun P, Rampal P, Barbier P, Isal J-P, Eriksson S, et al. Omeprazole (20 mg o.m.) versus ranitidine (150 mg b.i.d.) in reflux esophagitis. Results of a double-blind randomized trial. *Gastroentérologie Clinique et Biologique* 13: 457-462, 1989

Correspondence: *Donna McTavish*, Adis International Limited, 41 Centorian Drive, Private Bag, Mairangi Bay, Auckland 10, New Zealand.