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Omeprazole: a new drug for the treatment of acid-peptic diseases

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■ Omeprazole is the first of a new class of gastric antisecretory drugs, proton pump inhibitors. It inhibits the H^+,K^+-adenosinetriphosphatase enzyme of the gastric parietal cell, resulting in potent, long-lasting suppression of basal and stimulated acid secretion. The drug is currently approved for treatment of gastroesophageal reflux disease and Zollinger-Ellison syndrome. In clinical trials, treatment with omeprazole results in rapid healing of duodenal ulcers; it is also effective in treating gastric ulcer disease. It is uniformly well tolerated without significant adverse effects, although animal studies linked profound long-term suppression of gastric acid secretion with the development of gastric carcinoids. Potential future uses include the prophylaxis of ulceration secondary to stress or use of nonsteroidal anti-inflammatory drugs, and the prophylaxis of recurrent peptic ulcer disease.

▯ INDEX TERMS: OMEPRAZOLE, CLINICAL PHARMACOLOGY ▯ CLEVE CLIN J MED 1991; 58:418–427

■ **Editor's note: On June 19, 1991, omeprazole received US Food and Drug Administration approval for the short-term treatment of active duodenal ulcer disease.**

OMEPRAZOLE is the first of a new class of drugs, proton pump inhibitors, to be made available for the treatment of diseases in which acid-peptic injury plays a role. It produces more complete and longer-lasting suppression of gastric acid secretion than the histamine-2-receptor (H_2-receptor) antagonists, which have for years been the mainstay in the therapy of acid-peptic disorders. Omeprazole is currently approved by the Food and Drug Administration (FDA) for short-term treatment of erosive esophagitis and symptomatic gastroesophageal reflux which is resistant to standard medical therapy, as well as for the long-term treatment of pathological hypersecretory states such as Zollinger-Ellison syndrome and systemic mastocytosis.

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CLINICAL PHARMACOLOGY OF OMEPRAZOLE

Physiology of gastric acid secretion

Acid secretion takes place in the parietal cells of the stomach, which are located in the oxyntic glands of the fundus and corpus. These cells may be stimulated to secrete acid by three different pathways.[1] The neurocrine pathway involves the vagal release of acetylcholine, the paracrine pathway is mediated by the release of histamine from mast cells and enterochromaffin-like (ECL) cells in the stomach, and the endocrine pathway is mediated by the release of gastrin. Each of these transmitters has a specific receptor located on the basolateral surface of the parietal cell (*Figure 1*). Stimulation of these receptors leads to

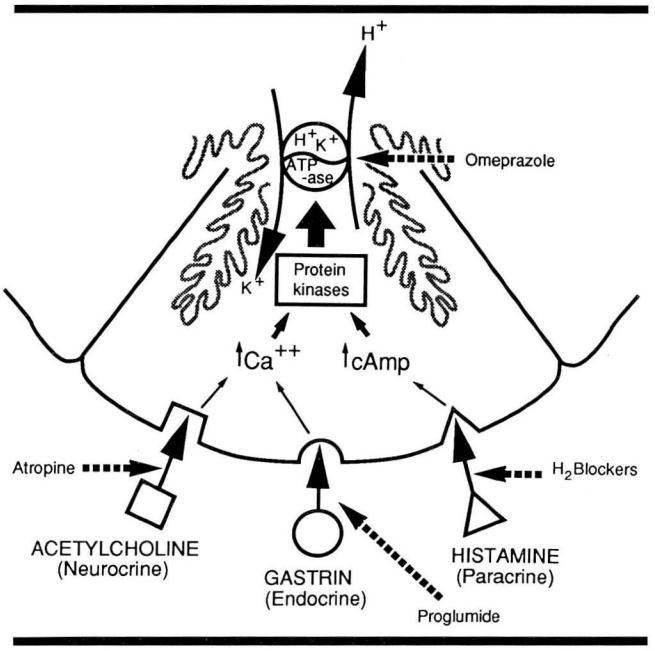

Figure 1. Schematic representation of acid secretion by the parietal cell. Dotted arrows indicate sites of action of various drugs that inhibit acid secretion.

activation of intracellular second messenger systems: histamine stimulates the production of cyclic adenosine monophosphate (cyclic AMP), while gastrin and acetylcholine promote the accumulation of intracellular calcium. These intracellular messengers then activate cyclic AMP-dependent and calcium-dependent protein kinases, which then stimulate the gastric proton pump (the H^+,K^+-adenosinetriphosphatase [ATPase] enzyme located at the apical surface of the parietal cell) to secrete hydrogen ions in exchange for potassium ions.

Mechanism of antisecretory activity

Omeprazole is a substituted benzimidazole (*Figure 2*). It inhibits the H^+,K^+-ATPase enzyme, thus blocking the final step of gastric acid secretion, regardless of the type of stimulation. This mechanism of action is very different from that of the commonly used H_2-receptor antagonists that reduce gastric acid secretion by inhibiting the H_2 receptor located on the basolateral membrane of the parietal cell.

Omeprazole is a weak base. This allows it to accumulate in the acidic environment of the parietal cell secretory canaliculus, where it is protonated and transformed into its active form, a sulphenamide derivative.

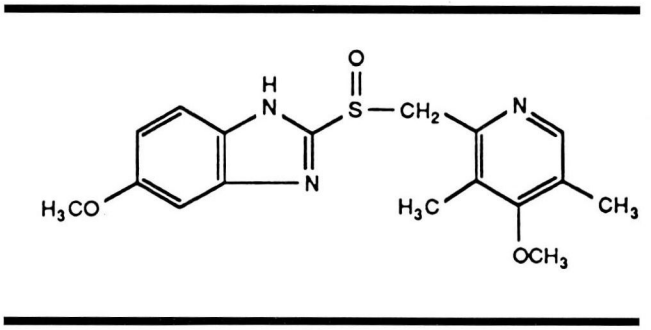

Figure 2. The chemical structure of omeprazole.

This compound then reacts with sulfhydryl groups on the H^+,K^+-ATPase enzyme, forming an inhibitory complex (*Figure 3*).[2] Omeprazole binds irreversibly to the enzyme,[3] resulting in long-lasting inhibition of gastric acid secretion (to restore gastric secretory activity, new enzyme must be synthesized). Because omeprazole acts at the final step of gastric acid secretion, it inhibits both basal and stimulated acid secretion.

Omeprazole's action is dose-dependent. Oral administration in single doses of 20, 40, 60, or 80 mg inhibited pentagastrin-stimulated gastric acid secretion by 36%, 63%, 90%, and 99% respectively.[4] Single oral doses of 20, 40, or 60 mg inhibited basal acid output by 29%, 81%, and 98%, respectively.[5] Doses of 10, 20, and 30 mg once daily for 1 week resulted in a decrease of 37%, 90%, and 97% in the 24-hour intragastric acidity of nine asymptomatic duodenal ulcer patients.[6]

With repeated oral doses, the antisecretory effects increase progressively during the first 3 to 5 days of drug administration.[4] In all likelihood, this is because the reduction of intragastric acidity decreases the degradation of the drug; thus it enhances its own bioavailability.

The duration of inhibition of acid secretion with omeprazole is long and dose-related. Twenty-four hours after single doses of 20 and 40 mg, pentagastrin-stimulated acid output was decreased by 26% and 48%, respectively; 3 days after the 40-mg dose, a 34% decrease in acid secretion was still seen.[4] Another group of patients was given 30 to 60 mg daily for 14 days. One week after completing the regimen, 24-hour intragastric acidity was decreased by 26%, with normalization seen at 8 weeks.[6]

Pharmacokinetics

Omeprazole is acid-labile and is formulated as enteric-coated granules in a hard gelatin capsule. Absorption is

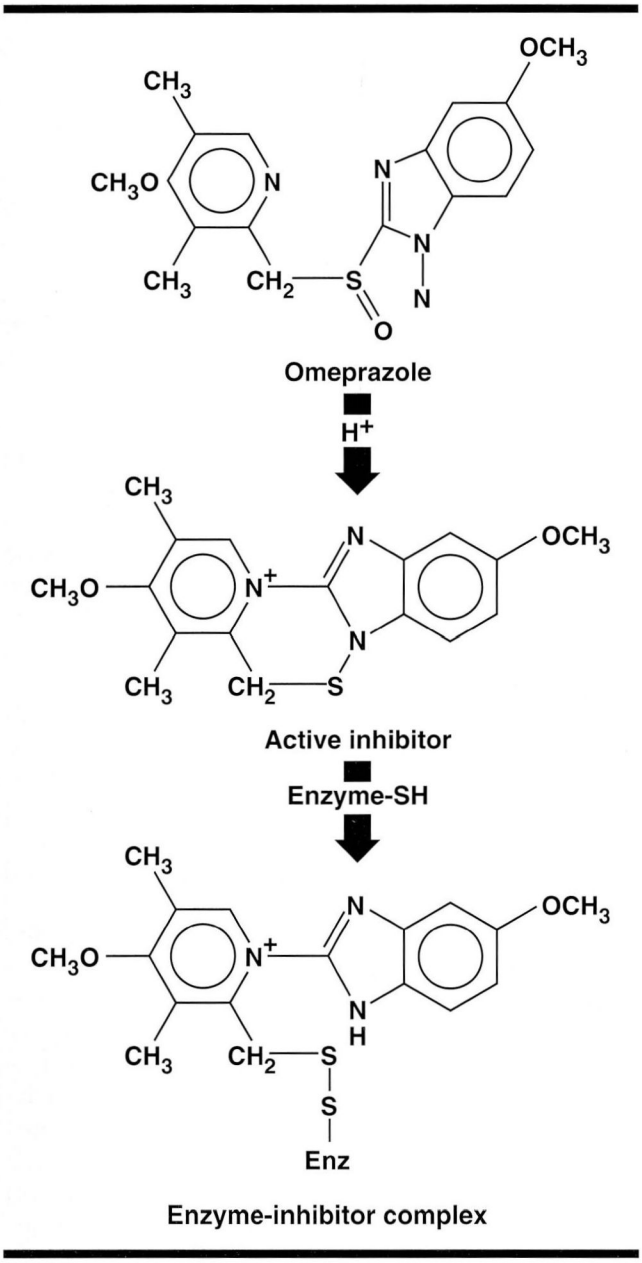

Figure 3. Acid-induced rearrangement of omeprazole into its active form, the sulphenamide that binds to the H^+,K^+-ATPase enzyme in the parietal cell. From Wallmark,[2] by permission.

rapid: peak plasma levels are reached 1 to 3 hours after oral administration.[7] Because first-pass hepatic metabolism is extensive, bioavailability after a single oral dose is only 35%, although this may increase to 60% with repeated doses.[7] As mentioned above, this increase coincides with the decrease in gastric acidity and probably reflects improved absorption due to this decrease.[8]

Drug elimination is rapid (half-life is 0.5 to 1 hour). While the degree of acid suppression is unrelated to plasma concentration, it does correlate with the area under the plasma concentration time curve, which reflects the amount of drug available to the parietal cell.[4] Omeprazole is completely metabolized in the liver. The metabolites are inactive and are excreted in the urine (80%) and feces (20%). The elimination of omeprazole metabolites is unaffected by impaired renal function but is decreased somewhat in elderly patients. In patients with impaired hepatic function, bioavailability is close to 100%.[7] The clinical significance of variability in metabolite elimination and bioavailability is uncertain, and no recommendations regarding dose alteration have been made for these patient populations.

SAFETY

Drug interactions

Omeprazole inhibits several monoxygenase reactions which are mediated by enzymes of the cytochrome P450 system (a family of enzymes in the liver involved in the oxidative metabolism of most drugs). Inhibition of these reactions impairs hepatic metabolism of diazepam, phenytoin, and warfarin.[9] Therefore, coadministration of omeprazole with these drugs should be done with care. Omeprazole also selectively induces a subfamily of cytochrome P450 which is involved in the metabolism of acetaminophen and polycyclic hydrocarbons.[10] Theoretically, this could increase the possibility of hepatotoxicity due to acetaminophen, and therefore some physicians advise care in administering omeprazole with acetaminophen.[11] More clinical data are required to clarify this issue. Omeprazole may also interfere with the absorption of drugs that require intragastric acidity for absorption, such as ketoconazole and iron salts.

Adverse effects

In trials involving more than 13,000 patients, omeprazole has been well tolerated. Serious adverse events were reported in 1% of patients, which is no more than with H_2-receptor antagonists or with placebo.[12] Minor symptoms such as nausea, diarrhea, headaches, dyspepsia, and dizziness have been described, but these also are no different from symptoms seen in patients receiving placebo or H_2-receptor antagonists. In addition, the adverse events observed do not increase with age and dose.

Carcinoid tumors

Initial enthusiasm over the potential applications of omeprazole was tempered by the discovery of gastric carcinoid tumors in rats that had been exposed to lifelong high doses of omeprazole.[13] The rats were treated over a 2-year period with 400 μmol/kg of omeprazole (a far greater dose than is used to treat acid-peptic disorders in humans). Results showed that 10% of the male rats and 40% of the female rats developed carcinoid tumors in the stomach.[13] The tumors consisted of ECL endocrine cells and appeared to progress in a continuum from diffuse ECL-cell hyperplasia to focal hyperplasia to focal carcinoids. The finding of carcinoid tumors in rats appears to be species-specific, as similar results have not been seen in other experimental models, such as the mouse or the dog.[13]

It appears that the development of these carcinoid tumors is not directly caused by omeprazole, but is related instead to a marked elevation in serum gastrin. Under normal conditions, gastrin release is inhibited by intragastric acidity, but the reduction of intragastric acidity caused by omeprazole results in the loss of this normal feedback inhibition.

In the rat, elevated gastrin levels (whether caused by omeprazole, high-dose ranitidine, or exogenous administration of gastrin) correlate with an increase in the proliferation rate and density of ECL cells in the stomach.[14–17] The ECL-cell changes are reversible: ECL-cell density returned to normal 20 weeks after cessation of therapy.[15] When the rats were antrectomized, thus eliminating the major endogenous source of gastrin, administration of omeprazole did not elevate plasma gastrin levels or increase ECL-cell density and proliferation rates, as compared with intact animals.[14–16]

In humans, gastric carcinoids are rare, accounting for only 3% to 5% of all gastrointestinal carcinoids and 0.3% of gastric tumors.[18] Gastric carcinoid tumors have been seen in patients with Zollinger-Ellison syndrome and pernicious anemia,[18,19] two naturally occurring states of hypergastrinemia. As in the animal model, ECL-cell density is related to serum gastrin levels in patients with atrophic gastritis, with the highest gastrin levels found in patients with carcinoid tumors.[20] This has led to the investigation of whether omeprazole influences gastrin levels and ECL-cell density in humans. In short-term studies, omeprazole increases fasting serum gastrin levels and 24-hour gastrin profiles to approximately two to five times pretreatment values.[21–24] The gastrin levels then return to normal within 2 weeks of completion of therapy.[23]

Longer-term studies of the effect of omeprazole on serum gastrin have yielded conflicting results. In a 1-year study, Koop found no increase in gastrin levels beyond a 3.6-fold rise seen after 1 month.[24] Lamberts found that gastrin levels increased significantly over the first 6 months of therapy, followed by no further increase for up to 2 years.[25] Jansen described a continued trend of further increases in gastrin over 2 years.[21]

In each of these studies, the greatest increase in gastrin level was in the first month of treatment, and correlated with the gastrin level prior to starting treatment when this information was available.[21,24] To put the gastrin data in perspective, patients with pernicious anemia have a 24-hour gastrin profile 30 times higher than untreated duodenal ulcer patients, while 28 days of omeprazole treatment increases the 24-hour gastrin profile only five times.[22]

Limited data are available on the effect of omeprazole on ECL-cell density in humans. In a short-term study, no significant increase in ECL-cell density was seen in a group of duodenal ulcer patients treated with omeprazole for 4 weeks.[26] In a 2-year study, the ECL-cell density increased during the first year of treatment in 10 patients without a further increase in the ensuing year. However, this finding could not be confirmed in a larger group of patients.[25]

The above animal and human data suggest that the extent and duration of acid suppression are the crucial determinants for the development of gastric carcinoids. There have been no reports of gastric carcinoids with omeprazole in the short-term treatment of acid-peptic diseases, and the short-term use of omeprazole in patients with peptic ulcer disease or gastroesophageal reflux disease does not seem to present a problem. However, the risks associated with continuous long-term omeprazole treatment in humans is not known at this time. It is therefore prudent to monitor serum gastrin levels in patients receiving chronic therapy with omeprazole, and to discontinue or reduce therapy if gastrin levels increase above five times the upper limit of normal.[27]

CLINICAL EFFICACY

Gastroesophageal reflux disease

While H_2-receptor antagonists consistently improve the symptoms of gastroesophageal reflux disease, the efficacy of these agents in the healing of erosive and ulcerative esophagitis is less clear. This class of drugs is of uniform benefit in the healing of peptic ulcer disease, but they heal no more than 60% of patients with

TABLE 1
HEALING RATES FOR OMEPRAZOLE IN GASTROESOPHAGEAL REFLUX DISEASE: RESULTS OF CONTROLLED TRIALS

Source	N	Regimen		% Healing	
		Drug	Dosage	4 wk	6 wk
Klinkenberg-Knol[30] (1987)	25	Omeprazole	60 mg	76*	88†
	26	Ranitidine	150 mg bid	27	38
Vantrappen[31] (1988)	26	Omeprazole	40 mg	85‡	96‡
	25	Ranitidine	150 mg bid	40	52
Havelund[32] (1988)	46	Omeprazole	40 mg	70§	85§
	42	Ranitidine	150 mg bid	26	44
Sandmark[33] (1988)	69	Omeprazole	20 mg	67¶	85¶
	75	Ranitidine	150 mg bid	31	50
Hetzel[29] (1988)	31	Omeprazole	20 mg/40mg	81¶	81¶
	32	Placebo		6	9

*P=0.002 †P =0.001 ‡P<0.01 §P not given ¶P<0.0001.

macroscopic esophagitis. Patients with severe gastroesophageal reflux disease are often treated with multiple medications for prolonged periods of time at considerable expense, and when this therapy fails, antireflux surgery is often necessary.

Omeprazole markedly decreased 24-hour acid exposure in a group of 12 patients with erosive esophagitis.[28] Prior to treatment, esophageal pH was <4 13.9% of the time in the upright position, 13.0% of the time in the supine position, and 14.1% of the time over the entire 24-hour period. After 3 weeks of therapy with omeprazole 20 mg daily, the corresponding values were significantly decreased to normal 24-hour acid exposure (2.5%, 0.1%, and 2.5%, respectively).

The efficacy of omeprazole in the treatment of gastroesophageal reflux disease has been studied in controlled clinical trials of patients with erosive or ulcerative esophagitis (*Table 1*). At doses of 20 or 40 mg once daily, omeprazole is clearly superior to placebo in the healing of erosive or ulcerative esophagitis.[29] At doses of 20, 40, and 60 mg, omeprazole is statistically superior to the H_2-receptor antagonist ranitidine after 4 or 8 weeks of therapy,[30–33] but the 60-mg dose does not appear to offer any advantage over the lower doses. Each of these studies also demonstrated a rapid and profound improvement in symptoms of gastroesophageal reflux disease (heartburn, regurgitation, and dysphagia) in comparison to the control agents. After 4 weeks of therapy, up to 85% of omeprazole-treated patients had no heartburn, compared with up to 42% of the ranitidine-treated patients.[31,33]

While the healing of macroscopic esophagitis with omeprazole is striking, this benefit is not seen in all patients. In most studies, 10% to 15% of patients do not heal with omeprazole. A major factor influencing healing is the initial severity of the esophagitis.[29,33] In Hetzel's multicenter study, the healing rate of patients with circumferential ulceration (the most severe grade of esophagitis) was only 44% after 4 weeks of treatment with omeprazole 40 mg and 56% at 8 weeks.[29]

Omeprazole is also effective in healing reflux esophagitis refractory to standard-dose H_2-receptor antagonist therapy. In a study of 98 patients with erosive esophagitis that was unhealed after 12 weeks of standard-dose therapy with cimetidine or ranitidine, omeprazole therapy (40 mg once daily) healed 90% of patients, compared with 47% of patients on high-dose ranitidine therapy (300 mg twice a day) ($P<0.0001$).[34]

Although omeprazole appears to be promising in the treatment of gastroesophageal reflux disease, successful therapy has not improved the high relapse rate typically seen after cessation of treatment.[29] An endoscopic relapse rate of 82% was seen 6 months after healing of erosive esophagitis in the multicenter study.[29] Long-term maintenance therapy with full-dose omeprazole has been studied in a limited number of patients in open uncontrolled trials. Omeprazole 20 mg once daily for 12 months in endoscopically healed patients has resulted in relapse rates of 26% to 34%.[35] The eventual role of omeprazole in the long-term maintenance therapy of gastroesophageal reflux disease is undergoing further study, and recommendations await additional data.

Omeprazole is superior to conventional doses of H_2-receptor antagonists in the relief of symptoms and healing of mucosal lesions in gastroesophageal reflux disease. With the advent of omeprazole, multi-drug therapy for gastroesophageal reflux disease may no longer be warranted.

Presently, omeprazole is approved by the FDA for 4 to 8 weeks of treatment of erosive or ulcerative esophagitis, or gastroesophageal reflux disease refractory to conventional therapy with H_2-receptor antagonists. Practical issues still unresolved include the safety of long-term treatment and, given the high relapse rate of esophagitis, the appropriate intervals for retreatment.

TABLE 2
HEALING RATES FOR OMEPRAZOLE IN DUODENAL ULCER DISEASE: RESULTS OF COMPARISON STUDIES

Source	N	Regimen		% Healing			
		Drug	Dosage	2 wk	4 wk	6 wk	8 wk
Classen[45] (1985)	146	Omeprazole	20 mg	72*	96	—	—
	160	Ranitidine	150 mg bid	59	92	—	—
Lauritsen[46] (1985)	67	Omeprazole	30 mg	73†	92*	—	—
	65	Cimetidine	1g	46	74	—	—
Bardhan[47] (1986)	34	Omeprazole	20 mg	83‡	94‡	—	100
	36	Omeprazole	40 mg	83‡	100‡	—	100
	35	Ranitidine	150 mg bid	53	82	—	94
Barbara[48] (1987)	61	Omeprazole	20 mg	66	97*	100*	—
	60	Ranitidine	150 mg bid	53	85	92	—
Archambault[49] (1988)	85	Omeprazole	20 mg	58	84	88	—
	84	Cimetidine	600 mg bid	46	80	89	—
Marks[50] (1988)	69	Omeprazole	20 mg	65§	97§	—	—
	66	Ranitidine	300 mg	39	81	—	—
Mulder[51] (1989)	91	Omeprazole	20 mg	63	91	—	—
	90	Ranitidine	150 mg bid	65	96	—	—
Cooperative Study Group[53] (1990)	94	Omeprazole	40 mg	68†	99†	—	100
	94	Ranitidine	150 mg bid	48	88	—	97
McFarland[52] (1990)	125	Omeprazole	20 mg	79¶	91*	—	—
	122	Ranitidine	300 mg	61	80	—	—

*P<0.05 †P<0.01 ‡P=0.007 § = "significantly better," P value not given ¶P<0.005

Zollinger-Ellison syndrome

Zollinger-Ellison syndrome accounts for approximately 0.1% of all patients with duodenal ulcer disease in the United States.[36] It is characterized by gastric acid hypersecretion due to a gastrin-producing tumor (typically located in the pancreas or duodenum or, on occasion, at distant sites) and results in many symptoms and complications: 90% of patients develop ulceration of the upper gastrointestinal tract,[36] while other less frequent symptoms include diarrhea and heartburn.

Control of gastric acid hypersecretion is central to the management of Zollinger-Ellison syndrome. This was formerly accomplished by total gastrectomy until the advent of H_2-receptor antagonists, which are highly effective in treating gastric acid hypersecretion. However, large doses are often needed at frequent intervals, and the amount of drug required for treatment often increases with time.[37]

In Zollinger-Ellison syndrome, acute therapy with omeprazole results in a profound decrease in gastric acid secretion.[37,38] In 11 patients treated with a single 60-mg dose of omeprazole, acid secretion was inhibited by 50% at 3 hours, 78% at 4 hours, and 86% at 8 hours after administration.[37] Gastric acid secretion was still inhibited by 80% at 24 hours after administration of omeprazole and by 50% at 48 hours after cessation of chronic therapy.

Chronic therapy with omeprazole for up to 5 years has uniformly resulted in continued inhibition of acid secretion, good symptom control, complete healing of any mucosal lesions, and lack of adverse effects.[37–41] In the largest study of the long-term efficacy of omeprazole in the treatment of Zollinger-Ellison syndrome, 40 patients followed for up to 51 months required an average dose of 82.5 mg daily to control acid secretion.[41] Only 6 patients required an increase in dosage during the study and 9 patients required twice-daily dosing.[41] The low incidence of tachyphylaxis has been confirmed in other studies, as dose requirements for most patients remain stable over time.[37–41]

Treatment of Zollinger-Ellison syndrome with omeprazole does not result in further elevation of gastrin levels.[38,40–42]

Thus, omeprazole should be regarded as the drug of choice for the therapy of gastric acid hypersecretion seen in Zollinger-Ellison syndrome. It is safe and effective and has the advantage of requiring fewer pills and dose-adjustments than H_2-receptor antagonists. The initial dose is typically 60 mg daily, which should then be titrated to a basal acid output (24 hours after the last dose) of <10 mEq per hour. (In Zollinger-Ellison

syndrome, symptoms alone are an unreliable guide to assess control of gastric acid secretion, and the presence of gastrointestinal pathology correlates with gastric acid secretion rates >10 mEq per hour.[42]) An intravenous formulation will soon be available for the perioperative control of acid secretion in Zollinger-Ellison syndrome patients.

Duodenal ulcer disease

H_2-receptor antagonists are the current mainstay of therapy for duodenal ulcer disease. They are well tolerated and, on average, heal 51%, 78%, and 92% of ulcers after 2, 4, and 8 weeks of therapy.[44] In randomized, controlled trials comparing omeprazole to standard doses of cimetidine or ranitidine, omeprazole is superior[45–48,50,52,53] or equivalent[49,51] in duodenal ulcer healing. The results of these trials are summarized in *Table 2*. Omeprazole has resulted in healing rates of 63% to 83% at 2 weeks and 91% to 100% at 4 weeks compared with healing rates of 46% to 65% at 2 weeks and 74% to 96% at 4 weeks with ranitidine or cimetidine.[45–48,50–53] Thus, omeprazole achieves healing rates at 4 weeks that are typically seen at 8 weeks with H_2-receptor antagonists. A daily 20-mg dose of omeprazole was used in most of these studies, and increasing the dose to 40 mg did not offer any therapeutic advantage.[47]

Healing rates for omeprazole are lower in North American studies than in studies performed overseas.[49,54] In the US study,[54] the healing rate was 41% at 2 weeks and 75% at 4 weeks, whereas in a Canadian study[49] the healing rates were 54% and 84% at the same time intervals. This is in contrast to the typical healing rate of better than 90% at 4 weeks seen in overseas trials. The reason for this difference is unknown.

In addition to accelerating the healing of duodenal ulcers, omeprazole typically relieves symptoms more rapidly than H_2-receptor antagonists,[47,49,51–53] but its impact on symptom relief is more variable than that seen with healing.

Despite the more profound suppression of acid secretion seen with omeprazole, duodenal ulcer relapse rates are no different than those seen after treatment with the H_2-receptor antagonists.[46,47,53]

The optimal dose and duration of omeprazole treatment in duodenal ulcer disease has yet to be determined but appears to be 20 mg once a day for 4 weeks. Increasing the dose to 40 mg may be useful in the treatment of ulcers refractory to conventional doses of H_2-receptor antagonists, although more data are needed. For typical duodenal ulcers, omeprazole may offer a modest advantage over conventional therapy at 4 weeks. Omeprazole has not yet received FDA approval for this indication.

Gastric ulcer disease

The results of trials comparing omeprazole to H_2-receptor antagonists in the treatment of gastric ulcers are summarized in *Table 3*. Inhibition of acid secretion with H_2-receptor antagonists results in average healing rates of 63%, 75%, and 88% after 4, 6, and 8 weeks of treatment.[44] In three of the five studies, healing rates achieved with omeprazole are equivalent but not superior to those seen with H_2-receptor antagonists.[55–59] In two trials, omeprazole at a dose of 20 mg once daily was superior to H_2-receptor antagonists at 4 weeks, but no differences were seen at 8 weeks.[57,58] In a study of 602 patients, Walan and associates demonstrated healing at 4 weeks in 69%, 80%, and 59% of patients treated with omeprazole 20 mg once daily, omeprazole 40 mg once daily, and ranitidine 150 mg twice daily, and in 89%, 96%, and 85% of patients at 8 weeks.[57] Omeprazole, 40 mg once daily was superior to the other regimens at both time intervals, and the 20-mg dose was superior to ranitidine at 4 weeks only. This study also showed that these differences in healing were maintained in those patients receiving concurrent therapy with nonsteroidal anti-inflammatory drugs (NSAIDs).

In three of the comparison trials, relief of ulcer symptoms was more rapid in the omeprazole-treated patients,[56–58] while no difference in symptom relief was seen in the other studies.[55,59] Recurrence rates of ulcers within 6 months of therapy are no different in patients treated with omeprazole or ranitidine.[57] As in other indications, omeprazole treatment has been uniformly well tolerated, with no reports of any significant adverse effects.

The efficacy of omeprazole in the treatment of gastric ulcer disease is less impressive than that seen in the other indications. The benefit of omeprazole in patients undergoing concurrent therapy with NSAIDs is of special clinical interest, but further trials are necessary. The role (if any) of omeprazole in gastric ulcer disease awaits the results of additional studies.

Resistant peptic ulcer disease

The role of omeprazole in the treatment of peptic ulcer disease resistant to conventional doses of H_2-receptor antagonists has been examined in open studies[60,61] and in a limited number of controlled tri-

TABLE 3
HEALING RATES FOR OMEPRAZOLE IN GASTRIC ULCER DISEASE: RESULTS OF COMPARISON STUDIES

Source	N	Regimen		% Healing			
		Drug	Dosage	2 wk	4 wk	6 wk	8 wk
Classen[55] (1985)	83	Omeprazole	20 mg	43	81	—	95
	74	Ranitidine	150 mg bid	45	80	—	90
Lauritsen[56] (1988)	90	Omeprazole	30 mg	54*	81	86	—
	86	Cimetidine	1g	39	73	78	—
Walan[57] (1989)	203	Omeprazole	20 mg	—	69*	—	89
	194	Omeprazole	40 mg	—	80†	—	96†
	205	Ranitidine	150 mg bid	—	59	—	85
Bate[58] (1989)	102	Omeprazole	20 mg	—	73*	—	84
	87	Cimetidine	400 mg bid	—	58	—	75
Danish Multicenter[59] (1989)	73	Omeprazole	30 mg	41	77	88	—
	73	Cimetidine	1g	41	58	82	—
Cooperative Study Group[53] (1990)	16	Omeprazole	40 mg	—	81	—	93
	24	Ranitidine	150 mg bid	—	58	—	87

*P<0.05. †P<0.0005.

als.[62–64] In a study of peptic ulcer disease patients who failed to heal after treatment with 450 to 600 mg of ranitidine for 3 or more months, omeprazole 40 mg once daily healed all 11 duodenal ulcer patients at 4 weeks, and it resulted in healing rates of 79% at 4 weeks and 95% at 8 weeks in 43 gastric ulcer patients.[61]

In a controlled trial, 107 patients with peptic ulcers (88 duodenal ulcers, 19 gastric ulcers) which were resistant to 8 weeks of standard-dose therapy with ranitidine or cimetidine were either continued on the same dose of the H_2-receptor antagonist or switched to omeprazole 40 mg once a day for up to 8 weeks.[62] Healing rates with omeprazole were 87% at 4 weeks and 98% at 8 weeks, whereas continued H_2-receptor antagonist therapy resulted in healing rates of 39% and 60% at the same intervals. These differences were significant at both time intervals. In a study of 50 duodenal ulcer patients who did not heal with high doses of cimetidine (2 or 3 g daily after 3 or more months), omeprazole 40 mg once daily again resulted in improved healing by 8 weeks, although the results were significant only for patients whose regimen had been cimetidine 3 g daily.[63] However, in another controlled trial of 151 duodenal ulcer patients who were unhealed after 6 weeks with conventional doses of cimetidine or ranitidine, omeprazole 20 mg offered no advantage over continued therapy with ranitidine 150 mg twice a day.[64] While more studies are clearly needed, omeprazole may well have a role in the therapy of resistant peptic ulcer disease prior to considering surgery.

CONCLUSIONS AND FUTURE PERSPECTIVES

The ultimate role of omeprazole in the treatment of acid-peptic disorders remains to be determined. Currently approved and potential future clinical applications for omeprazole are listed in *Table 4*. Omeprazole represents a major advance in the treatment of gastroesophageal reflux disease and Zollinger-Ellison syndrome. Approval can be anticipated for the treatment of duodenal ulcer disease shortly and for gastric ulcer disease over the next several years.

While omeprazole is safe and well tolerated in all short-term studies, uncertainty persists with respect to the long-term consequences of hypergastrinemia caused by profound acid suppression, and additional studies are needed to address this concern.

Weekend or intermittent therapy is one option that is being examined to avoid this problem. Weekend therapy with omeprazole at a dose of 20 mg in a limited number of patients has resulted in either slight or no increase in basal gastrin levels, and slight increases in meal-stimulated gastrin levels after 4 to 8 weeks of therapy.[65,66] However, after 4 days without treatment, basal and peak acid outputs had reverted to the pretreatment values.[65] No trials examining the clinical efficacy of weekend-only therapy in acid-peptic disorders have been published to date.

Additional clinical applications will undoubtedly come in the areas of prophylaxis of stress-induced gastropathy in critically ill patients, recurrent duodenal ulcer disease, and ulceration induced by NSAIDs. A recent preliminary study with intravenous

TABLE 4
CLINICAL APPLICATIONS OF OMEPRAZOLE

FDA approved applications
Gastroesphageal reflux disease
Zollinger-Ellison syndrome
FDA approval pending
Duodenal ulcer disease
Gastric ulcer disease
Under investigation
Prophylaxis for nonsteroidal antiinflammatory drug-induced gastropathy
Prophylaxis for stress-induced gastropathy
Gastrointestinal bleeding from peptic ulcer disease
Sclerotherapy induced esophageal ulceration
Noncardiac chest pain

omeprazole in patients with actively bleeding peptic ulcers demonstrated cessation of bleeding in 84% of the omeprazole-treated group, compared with 15% in a group treated with ranitidine (therapy with H_2-receptor antagonists does not appear to be effective in the treatment of actively bleeding peptic ulcers).[67]

Esophageal ulceration after endoscopic sclerotherapy of esophageal varices may be resistant to standard therapy with H_2-receptor antagonists and sucralfate. In an open study with omeprazole 40 mg daily in 10 such patients, complete healing was seen in each patient after 8 weeks.[68]

Therapeutic applications of omeprazole in the areas of non-cardiac chest pain and non-ulcer dyspepsia can also be anticipated as efforts continue to examine the role of acid in the pathogenesis of both of these disorders.

Therapy with omeprazole is at present quite expensive. In Cleveland, the wholesale cost of omeprazole is $92 for 30 days of therapy at a dose of 20 mg daily, compared with $56 to $79 for standard doses of H_2-receptor antagonists for the same duration. In spite of the expense, however, omeprazole is clearly more cost-effective than treatment with multiple drugs or higher-than-normal doses of H_2-receptor antagonists in gastroesophageal reflux disease. In duodenal ulcer disease, the shorter course of therapy with omeprazole may prove to be a cost advantage as well.

REFERENCES

1. Wolfe MM, Soll AH. The physiology of gastric acid secretion. N Engl J Med 1988; **319**:1707–1715.
2. Wallmark B. Omeprazole: mode of action and effect on acid secretion in animals. Scand J Gastroenterol 1989; **24(suppl 166)**:12–18.
3. McGuigan JE. Inhibition of hydrogen-potassium-stimulated adenosine triphosphatase: effects on acid secretion, plasma gastrin, and the gastric mucosa (editorial). Gastroenterology 1989; **97**:1045–1048.
4. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. Gut 1983; **24**:270–276.
5. Lind T, Cederberg C, Ekenved G, Olbe L. Inhibition of basal and betazole- and sham-feeding-induced acid secretion by omeprazole in man. Scand J Gastroenterol 1986; **21**:1004–1010.
6. Sharma BK, Walt RP, Pounder RE, Gomes M, Wood EC, Logan LH. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. Gut 1984; **25**:957–964.
7. Cederberg C, Andersson T, Skanberg I. Omeprazole: pharmacokinetics and metabolism in man. Scand J Gastroenterol 1989; **24(Suppl 166)**:33–40.
8. Prichard PJ, Yeomans ND, Mihaly GW, et al. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology 1985; **88**:64–69.
9. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism. Studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. Gastroenterology 1985; **89**:1235–1241.
10. Diaz D, Fabre I, Daujat M, et al. Omeprazole is an aryl hydrocarbon-like inducer of human hepatic cytochrome P450. Gastroenterology 1990; **99**:737–747.
11. Farrell GC, Murray M. Human cytochrome P450 isoforms: their genetic heterogeneity and induction by omeprazole (editorial). Gastroenterology 1990; **99**:885–889.
12. Solvell L. The clinical safety of omeprazole. Scand J Gastroenterol 1989; **24(suppl 166)**:106–110.
13. Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C. Toxicological studies on omeprazole. Scand J Gastroenterol 1985; **20(suppl 108)**:53–69.
14. Larsson H, Carlsson E, Mattsson H, et al. Plasma gastrin and gastric enterochromaffinlike cell activation and proliferation. Studies with omeprazole and ranitidine in intact and antrectomized rats. Gastroenterology 1986; **90**:391–399.
15. Larsson H, Carlsson E, Hakanson R, 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 1988; **95**:1477–1486.
16. Ryberg B, Tielemans Y, Axelson J, et al. Gastrin stimulates the self-replication rate of enterochromaffinlike cells in the rat stomach. Effects of omeprazole, ranitidine, and gastrin-17 in intact and antrectomized rats. Gastroenterology 1990; **99**:935–942.
17. Tielemans Y, Hakanson R, Sundler F, Willems G. Proliferation of enterochromaffinlike cells in omeprazole-treated hypergastrinemic rats. Gastroenterology 1989; **96**:723–729.
18. Borch K, Renvall H, Liedberg G. Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anemia. Gastroenterology 1985; **88**:638–648.
19. Carney JA, Go VLW, Fairbanks VF, Moore SB, Alport EL, Nora FE. The syndrome of gastric argyrophil carcinoid tumors and nonantral gastric atrophy. Ann Intern Med 1983; **99**:761–766.
20. Borch K, Renvall H, Liedberg G, Andersen BN. Relations between circulating gastrin and endocrine cell proliferation in the atrophic gastric fundic mucosa. Scand J Gastroenterol 1986; **21**:357–363.
21. Jansen JBMJ, Klinkenberg-Knol EC, Meuwissen SGM, et al. Effect of long-term treatment with omeprazole on serum gastrin and serum group A and C pepsinogens in patients with reflux esophagitis. Gastroenterology 1990; **99**:621–628.
22. Lanzon-Miller S, Pounder RE, Hamilton MR, et al. Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidien or omeprazole. Aliment Pharmacol Therap 1987; **1**:239–251.
23. Karnes WE, Berlin RG, Maxwell V, Sytnik B, Root JK, Walsh JH. Prolonged inhibition of acid secretion causes hypergastrinemia without altering pH inhibition of gastrin release in humans. Aliment Pharmacol Therap 1990; **4**:443–456.
24. Koop H, Klein M, Arnold R. Serum gastrin levels during long-term omeprazole treatment. Aliment Pharmacol Therap 1990; **4**:131–138.

25. Lamberts R, Creutzfeldt W, Stockmann F, Jacubaschke U, Maas S, Brunner G. Long-term omeprazole treatment in man: effects on gastric endocrine cell populations. Digestion 1988; **39:**126–135.
26. Helander HF. Oxyntic mucosa histology in omeprazole-treated patients suffering from duodenal ulcer or Zollinger-Ellison syndrome. Digestion 1986; **35(suppl 1):**123–129.
27. Creutzfeldt W, Lamberts R, Stockmann F, Brunner G. Quantitative studies of gastric endocrine cells in patients receiving long-term treatment with omeprazole. Scand J Gastroenterol 1989; **24(suppl 166):**122–128.
28. Ruth M, Enbom H, Lundell L, Lonroth H, Sandberg N, Sandmark S. The effect of omeprazole or ranitidine treatment on 24-hour esophageal acidity in patients with reflux esophagitis. Scand J Gastroenterol 1988; **23:**1141–1146.
29. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988; **95:**903–912.
30. Klinkenberg-knol EC, Jansen JMBJ, Fetsen HPM, Meuwissen SGM, Lamers CBHW. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. Lancet 1987; **1:**349–351.
31. Vantrappen G, Rutgeerts L, Schurmans P, Coenegrachts JL. Omeprazole (40 mg) is superior to ranitidine in short-term treatment of ulcerative reflux esophagitis. Dig Dis Sci 1988; **33:**523–529.
32. Havelund T, Laursen LS, Skoubo-Kristensen E, et al. Omeprazole and ranitidine in treatment of reflux esophagitis: double blind comparative trial. Br Med J 1988; **296:**89–92.
33. Sandmark S, Carlsson R, Fausa O, Lundell L. Omeprazole or ranitidine in the treatment of reflux esophagitis. Results of a double blind, randomized Scandanavian multicenter study. Scand J Gastroenterol 1988; **23:**625–632.
34. Lundell L, Backman L, Ekstrom P, 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. Aliment Pharmacol Therap 1990; **4:**145–155.
35. Klinkenberg-Knol EC, Jansen JBMJ, Lamers CBHW, Nelis F, Snel P, Meuwissen SGM. Use of omeprazole in the management of reflux oesophagitis resistant to H_2-receptor antagonists. Scand J Gastroenterol 1989; **24 (suppl 166):**88–93.
36. Wolfe MM, Jensen RT. Zollinger-Ellison syndrome. Current concepts in diagnosis and management. N Engl J Med 1987; 317:1200–1209.
37. McArthur KE, Collen MJ, Maton PN, et al. Omeprazole: effective, convenient therapy for Zollinger-Ellison syndrome. Gastroenterology 1985; **88:**939–944.
38. Lamers CBHW, Lind T, Moberg S, Jansen JBMJ, Olbe L. Omeprazole in Zollinger-Ellison Syndrome. Effects of a single dose and of long-term treatment in patients resistant to histamine H_2-receptor antagonists. N Engl J Med 1984; **310:**758–761.
39. Bardram L, Stadil F. Effects of omeprazole on acid secretion and acid-related symptoms in patients with Zollinger-Ellison syndrome. Scand J Gastroenterol 1989; **24(suppl 166):**95–100.
40. Delchier JC, Soule JC, Mignon M, et al. Effectiveness of omeprazole in seven patients with Zollinger-Ellison syndrome resistant to histamine H_2-receptor antagonists. Dig Dis Sci 1986; **31:**693–699.
41. Maton PN, Vinayek R, Frucht H, et al. Long-term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a prospective study. Gastroenterology 1989; **97:**827–836.
42. Maton PN, Lack EE, Collen MJ, et al. The effect of Zollinger-Ellison syndrome and omeprazole therapy on gastric oxyntic endocrine cells. Gastroenterology 1990; **99:**943–950.
43. Raufman JP, Collins SM, Pandol SJ, et al. Reliability of symptoms in assessing control of gastric acid secretion in patients with Zollinger-Ellison syndrome. Gastroenterology 1983; **84:**108–113.
44. Feldman M, Burton ME. Histamine$_2$-receptor antagonists. Standard therapy for acid-peptic diseases. N Engl J Med 1990; **323:**1749–1755.
45. Classen M, Dammann HG, Domschke W, et al. Omeprazole heals duodenal, but not gastric ulcers more rapidly than ranitidine. Results of two German multicentre trials. Hepato-gastroenterol 1985; **32:**243–245.
46. Lauritsen K, Rune SJ, Bytzer P, et al. Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. N Engl J Med 1985; **312:**958–961.
47. Bardhan KD, Bianchi Porro G, Bose K, et al. A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. J Clin Gastroenterol 1986; **8:**408–413.
48. Barbara L, Blasi A, Cheli R, et al. Omeprazole vs ranitidine in the short-term treatment of duodenal ulcer: an Italian multicenter study. Hepato-gastroenterol 1987; **34:**229–232.
49. Archambault AP, Pare P, Bailey RJ, et al. Omeprazole (20 mg daily) versus cimetidine (1200 mg daily) in duodenal ulcer healing and pain relief. Gastroenterology 1988; **94:**1130–1134.
50. Marks IN, Winter TA, Lucke W, et al. Omeprazole and ranitidine in duodenal ulcer healing. S Afr Med J 1988; **74(Suppl):**54–56.
51. Mulder CJJ , Tijtgat GNJ , Cluysenaer OJJ , et al. Omeprazole (20 mg o.m.) versus ranitidine (150 mg b.d.) in duodenal ulcer healing and pain relief. Aliment Pharmacol Therap 1989; **3:**445–451.
52. McFarland RJ, Bateson ML, Green JRB, et al. Omeprazole provides quicker symptom relief and duodenal ulcer healing than ranitidine. Gastroenterology 1990; **98:**278–283.
53. Cooperative study group. Double blind comparative study of omeprazole and ranitidine in patients with duodenal or gastric ulcer: a multicentre trial. Gut 1990; **31:**653–656.
54. Graham DY, McCullough A, Sklar M, et al. Omeprazole versus placebo in duodenal ulcer healing. The United States experience. Dig Dis Sci 1990; **35:**66–72.
55. Classen M, Dammann G, Domschke W, et al. Healing rates following omeprazole and ranitidine treatment of gastric ulcer. Results of a German multicenter study. Dtsch Med Wochenschr 1985; **110:**628–633.
56. Lauritsen K, Rune SJ, Wulff HR, et al. Effect of omeprazole and cimetidine on prepyloric gastric ulcer: double blind comparative trial. Gut 1988; **29:**249–253.
57. Walan A, Bader JP, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989; **320:**69–75.
58. Bate CM, Wilkinson SP, Bradby GVH, et al. Randomized, double blind comparison of omeprazole and cimetidine in the treatment of symptomatic gastric ulcer. Gut 1989; **30:**1323–1328.
59. Danish Omeprazole Study Group. Omeprazole and cimetidine in the treatment of ulcers of the body of the stomach: a double blind comparative trial. Br Med J 1989; **298:**645–647.
60. Pen JH, Michielsen PP, Pelckmans PA, Van Maercke YM. Omeprazole in the treatment of H_2-resistant gastroduodenal ulcers (abstract). Gastroenterology 1988; **94:**A348.
61. Brunner G, Lreutzfeldt W, Harke U, Lamberts R. Therapy with omeprazole in patients with peptic ulcerations resistant to extended high-dose ranitidine treatment. Digestion 1988; **39:**80–90.
62. Bardhan KD, Naesdal J, Bianchi Porro G, et al. Omeprazole in the treatment of refractory peptic ulcer (abstract). Gastroenterology 1988; **94:**A22.
63. Bardhan KD, Dhande D, Hinchliffe RFL, et al. Omeprazole in the treatment of ultra refractory duodenal ulcer (abstract). Gastroenterology 1988; **94:**A22.
64. Delchier JL, Isal JP, Eriksson S, Soule JL. Double blind multicentre comparison of omeprazole 20 mg once daily versus ranitidine 150 mg twice daily in the treatment of cimetidine or ranitidine resistant duodenal ulcers. Gut 1989; **30:**1173–1178.
65. Hewson EG, Yeomans ND, Angus PW, et al. Effect of weekend therapy with omeprazole on basal and stimulated acid secretion and fasting plasma gastrin in duodenal ulcer patients. Gut 1988; **29:**1715–1720.
66. Crobach LFSJ, Jansen JBMJ, Lamers CBHW. Effect of intermittent weekend therapy with omeprazole on basal and postprandial serum gastrin concentrations in patients with duodenal ulcer. Clin Pharmacol Ther 1988; **43:**643–647.
67. Brunner G, Chang J. Intravenous therapy with high doses of ranitidine and omeprazole in critically ill patients with bleeding peptic ulcerations of the upper intestinal tract: an open randomized trial. Digestion 1990; **45:**217–225.
68. Gimson A, Polson R, Westaby D. Omeprazole in the managment of intractable esophageal ulceration following injection sclerotherapy. Gastroenterology 1990; **99:**1829–1831.