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REVIEW ARTICLE

Omeprazole
Overview and Opinion

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Omeprazole, a substituted benzimidazole, is a specific inhibitor of the enzyme H^+/K^+-ATPase, which is found on the secretory surface of the parietal cell. This enzyme, the "proton pump," catalyzes the final step in acid secretion. Omeprazole is a powerful inhibitor of gastric acid secretion. At the time of writing, omeprazole has been licensed in the United States for the treatment of severe grades of gastroesophageal reflux disease (GERD) as well as GERD unresponsive to treatment with currently available agents, and for the treatment of Zollinger-Ellison syndrome and other gastric hypersecretory states. Most recently, it has been recommended by the FDA advisory committee for approval as first-line therapy in duodenal ulcer disease.

KEY WORDS: Omeprazole; clinical pharmacology; therapeutics; H_2-receptor antagonists; meta-analysis.

Omeprazole, a substituted benzimidazole, is a specific and noncompetitive inhibitor of the enzyme H^+/K^+-ATPase, known as the gastric proton pump. It thereby produces a profound and prolonged suppression of gastric acid secretion. By virtue of its potency in reducing acid secretion, it may provide more effective treatment for acid-related disease in the upper gastrointestinal tract.

Omeprazole has undergone extensive research and development in Europe by Astra Pharmaceuticals. More recently, it has been launched in the United States under license by Merck, Sharp & Dohme (West Point, Pennsylvania). In the United States, its approved indications are the short-term treatment of duodenal ulcer, severe or refractory gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome, and other hypersecretory states. As of May 1990, omeprazole was licensed in 38 other countries worldwide.

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The objective of this review is to highlight aspects of the clinical pharmacology and efficacy of omeprazole with a view to placing the drug into current perspective for the treatment of acid-related disease.

PHARMACOLOGY OF OMEPRAZOLE

The enzyme H^+/K^+-ATPase, located in the secretory canaliculi of parietal cells, actively secretes hydrogen ions in exchange for potassium ions. It is unique in its site and action (1–3). During parietal cell activation, intracytoplasmic vesicles containing H^+/K^+-ATPase fuse with the apical membrane and its secretory canaliculi, exposing the enzyme to the gastric lumen.

Omeprazole is a lipophilic weak base with an approximate pKa of 4. Autoradiographic studies in the mouse have shown that [^{14}C]omeprazole is widely distributed within 5 min of intravenous administration. However, 16 hr later, omeprazole is virtually confined to parietal cells within the gastric mucosa (3).

In the presence of acid within the secretory canaliculi of the parietal cell, omeprazole becomes protonated and, therefore, charged. In this form, it is unable to diffuse back across the cell membrane

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and so becomes localized in the acidic space of the secretory canaliculi. Here, omeprazole is converted to its active form, a sulfenamide, which forms a sulfhydryl bond with membrane-bound H^+/K^+-ATPase to which it attaches from the luminal aspect of the cell membrane. This reaction irreversibly inactivates the enzyme.

Inhibition of H^+/K^+-ATPase by omeprazole blocks the final common pathway for gastric acid secretion (4). This site of drug action contrasts with other available antisecretory agents including H_2-receptor antagonists and anticholinergics, which act at receptors on the basolateral aspect of the parietal cell (5). Omeprazole blocks the response of H^+/K^+-ATPase to extracellular stimuli as well as to intracellular cyclic adenosine monophosphate (cAMP) which is a second messenger in the parietal cell (4–7).

PHARMACOKINETICS IN MAN

Omeprazole is unstable in conditions of low pH and so must be protected from the effects of gastric acid when given orally. It is therefore administered as capsules containing enteric-coated granules of the drug. Absorption commences in the duodenum and peak plasma concentrations are achieved by 2 hr (8, 9). Omeprazole has a plasma half-life of around 1 hr (8). Its pharmacological effect is, however, much more prolonged and so a once daily dosing regimen is employed. The degree of absorption of omeprazole increases during the first few days of treatment (9). The most likely explanation for this is that omeprazole progressively suppresses acid secretion over the first few days. Therefore, as less acid is present in the stomach as further doses of omeprazole are taken, less omeprazole is degraded and so more can be absorbed. Food may slow the rate of omeprazole absorption without reducing the total amount absorbed (10).

Omeprazole is about 95% protein-bound, mainly to albumin and α_1-acid glycoprotein (8). It undergoes extensive metabolism by the liver. Its metabolites—a sulfide, a sulfone and two hydroxyomeprazoles—are mainly excreted in the urine, but around 20% is recovered in feces from biliary secretion (8).

In patients with chronic renal failure, plasma omeprazole concentrations are similar to those observed in healthy volunteers (11, 12). Clearance of omeprazole is reduced in patients with cirrhosis (13, 14), but there is no drug accumulation with once daily dosing.

PHARMACODYNAMICS IN MAN

Omeprazole produces prolonged but reversible reduction of gastric acidity. Five days after stopping the drug, there is recovery of acid secretion without evidence of rebound hypersecretion (15). The onset of action of omeprazole is within 1 hr of oral administration but is maximal at about 6 hr (16). Its effective duration of action is in excess of 24 hr (15, 17–19). Omeprazole 20 mg taken in the morning reduces 24-hr intragastric acidity by around 90%, while conventional doses of currently available H_2-receptor antagonists reduce 24-hr intragastric acidity by 37–68% (20). If the H_2-receptor antagonists are given as single nocturnal doses, they reduce overnight acidity by 79–95%; omeprazole 20 mg as a single morning dose reduces overnight acidity by 88% (20).

During treatment with omeprazole, intragastric concentrations of bacteria, nitrite, and *N*-nitroso compounds are temporarily increased (21). A similar finding has been noted during treatment with other gastric antisecretory agents such as cimetidine (22). To date, there is no evidence that the mild increase in *N*-nitroso compounds found during treatment with acid-inhibiting drugs in any way increases the risk of gastric cancer (23, 24).

Omeprazole has no effect on the handling of acid or electrolytes by the kidneys (25). Omeprazole only slightly reduces pepsinogen secretion (26, 27), but peptic activity is markedly reduced by omeprazole because pepsinogen is largely biologically inactive at the levels of pH that omeprazole produces. Secretion of intrinsic factor by parietal cells is unaffected by omeprazole (28, 29).

Omeprazole does not affect secretion of gastrointestinal peptides apart from gastrin (30). Its effects on gastrin are discussed in more detail below. Plasma levels of a variety of other hormones including thyroxine, triiodothyronine, cortisol, testosterone, gonadotrophins, and prolactin are unaffected by omeprazole (31, 32).

Omeprazole has been shown not to affect gastric emptying (33), esophageal peristalsis, or lower esophageal sphincter pressure (34, 35).

OMEPRAZOLE AND GASTRIN

Inhibition of acid secretion increases intragastric pH, resulting in an increased release of gastrin from

antral G cells. Gastrin is trophic to the gastric mucosa. Hypergastrinemia could theoretically predispose to ulcer recurrence after healing because of an increased parietal cell mass and maximal acid output. However, current evidence suggests that ulcer recurrence is not increased after treatment with omeprazole (36, 37). Hypergastrinemia induced by omeprazole is temporary and reverses when acid secretion returns to normal (38).

Lifelong toxicological studies performed in rats given high doses of omeprazole have demonstrated a dose-dependent, reversible hyperplasia of the gastric mucosa associated with marked hypergastrinemia (39, 40). Specifically, since gastrin is trophic to enterochromaffin-like (ECL) cells, increases in the numbers of these cells have been reported. Trophic effects of gastrin on rat gastric ECL cells also have produced micronodules and nonmetastasizing gastric carcinoid tumors composed of these cells (39, 40). Such changes have been observed in female rats fed lifelong with very high doses of omeprazole. ECL cell hyperplasia in the rat also can be produced by chronic administration of high-dose ranitidine sufficient to cause a marked increase in circulating gastrin levels (41).

Although the finding of ECL cell hyperplasia in rats fed high doses of omeprazole or ranitidine has given rise to concern in the minds of some investigators regarding the safety of acid-suppressing drugs, the true clinical relevance of these findings may have been overemphasized. The observed ECL cell hyperplasia is almost certainly an effect of hypergastrinemia and is not due to any particular drug (42).

There are major structural and functional differences between the ECL cells of rat and human gastric mucosa. In the rat, the ECL cell is the principal site for the synthesis and storage of gastric mucosal histamine; the role of this cell in man is unclear, but it does not contain large amounts of histamine. ECL cell hyperplasia in response to hypergastrinemia is more likely to develop in the rat than in other species because rats have a proportionately greater gastrin response to acid inhibition, a greater sensitivity of the ECL cell to hypergastrinemia, and a higher ECL cell density in gastric mucosa (42). Surgical resection of about 75% of the acid-producing gastric mucosa of the rat with retention of the gastric antrum has produced sustained hypergastrinemia associated with the development of ECL cell hyperplasia and carcinoid tumors composed of ECL cells in the gastric remnant (43). In a separate experiment, resection of the gastric antrum, which contains the population of gastrin-secreting G cells, prevented the development of ECL cell hyperplasia in rats given high-dose omeprazole or ranitidine (41). Hypergastrinemia and ECL cell hyperplasia induced by omeprazole are reversible on stopping the drug (44).

Spontaneously occurring gastric ECL cell carcinoids, similar to those encountered in the rat toxicology studies, are rare in man but have been observed in patients with pernicious anemia or Zollinger-Ellison syndrome (45, 46). Both these conditions are, of course, associated with marked hypergastrinemia that may be many times higher than levels produced by antisecretory drugs. No changes in gastric mucosal histology or in ECL cell density have been observed in over 1000 patients receiving omeprazole continuously for over six years (47–50).

Sequential measurements of plasma gastrin levels and gastric ECL cell density have been made in several clinical studies of omeprazole. These studies have shown a modest elevation in plasma gastrin levels, maximal at about one month of treatment (47, 48, 51). Chronic treatment with high doses of omeprazole (40–80 mg daily) in patients with severe refractory peptic ulceration or Zollinger-Ellison syndrome has not produced any further elevation in gastrin above the existing elevated levels (52) or any increases in ECL cell density (47–50).

GENOTOXICITY

Recently, concerns have been raised about possible genotoxic effects of omeprazole. In an experiment performed by workers at Glaxo Laboratories, the incorporation of tritiated thymidine into the DNA of gastric mucosal cells was studied after administration to rats of single doses of omeprazole 20–30 mg/kg (53). Both the methodology of this experiment and the interpretation of the results have been heavily criticized (54–56). Important experimental controls were lacking, and the cell separation techniques employed were inadequate. The significance of these findings and their implications for future research are discussed in greater detail in an editorial to be published in this journal.

OMEPRAZOLE IN CLINICAL PRACTICE

Clinical Safety. By May of 1990, over 19,000 individuals had received omeprazole in clinical studies. Generally, it has been well tolerated and no

TABLE 1. METAANALYSIS OF COMPARATIVE STUDIES BETWEEN OMEPRAZOLE AND H_2-RECEPTOR ANTAGONISTS IN DUODENAL ULCER

	% healed (95% CI)			
	Two weeks		*Four weeks*	
	Omeprazole	*Ranitidine*	*Omeprazole*	*Ranitidine*
Omeprazole 20 mg daily vs ranitidine 300 mg daily (reference 63–72)	69.3 (66.4–72.2)	52.8 (49.7–55.9)	92.8 (91.1–94.5)	83.1 (80.7–85.5)
	difference = 16.5%** (95% CI = 12.5–20.7)		difference = 9.7%** (95% CI = 6.7–12.7)	
	Omeprazole	*Cimetidine*	*Omeprazole*	*Cimetidine*
Omeprazole 20 mg daily vs cimetidine 800 mg daily (references 73–78)	64.1 (60.3–67.9)	43.1 (39.3–46.9)	90.4 (88.0–92.8)	77.7 (74.4–81.0)
	difference = 21.0%** (95% CI = 15.6–26.4)		difference = 12.7% (95% CI = 8.6–16.8)	

**$P < 0.001$ Mantel-Haenszel chi-squared test.

serious adverse effects have been reported. The overall incidence of mild adverse effects is also low and, in comparative studies, has been in the same range as reported for H_2-receptor antagonists (50). A degree of caution is, of course, essential for any new drug and extensive postmarketing surveillance studies are currently being conducted with omeprazole.

Drug Interactions. Omeprazole is metabolized by cytochrome P-450 and has the potential to interact with certain drugs also metabolized by this system (57). Omeprazole's binding affinity to this system is similar to that of cimetidine on a weight-for-weight basis but the therapeutic dose of omeprazole is much lower.

Omeprazole does not alter the pharmacokinetics of oral propranolol (58). It does interact with the R enantiomer of warfarin (59), so blood coagulation should be closely monitored if these two drugs are taken together. Omeprazole significantly slows the elimination of diazepam (60), but since there is a wide therapeutic index for this drug and other benzodiazepines, clinically significant interactions are unlikely. There is a potentially important interaction between omeprazole and phenytoin (diphenyl hydantoin), which has a much lower therapeutic index (61, 62). Patients on this drug who are given omeprazole may develop frank toxicity.

Omeprazole in Duodenal Ulcer. Omeprazole recently has received FDA approval for use in the short-term, first-line treatment of duodenal ulceration in the United States. In double-blind trials, omeprazole 20 mg daily has produced higher healing rates than either ranitidine (63–72) or cimetidine (73–78). Omeprazole also has been associated with a more rapid resolution of symptoms than H_2-receptor antagonists (eg, 70).

A metaanalysis of overall healing rates on omeprazole and H_2-receptor antagonists is presented in Table 1. In comparisons of omeprazole and ranitidine, the data presented in Table 1 are derived from 999 patients on omeprazole and 1009 on ranitidine. Comparative studies of omeprazole and cimetidine in Table 1 include 624 patients on omeprazole and 648 on cimetidine. Such combined data from controlled clinical trials confirm the superiority of omeprazole over the H_2-receptor antagonists in healing duodenal ulcer.

Healing rates for omeprazole in United States trials in duodenal ulcer have been lower than those observed in European trials (79). Part of the explanation for this may be that patients attending tertiary referral centers because of a severe uler diathesis have been included in American trials. With this in mind, it is of interest to note that the healing rate on placebo in at least one such trial was also lower than is usually seen (79). The efficacy of omeprazole in duodenal ulcer should be further examined in clinical trials in the United States within an ambulatory setting.

Omeprazole in Gastric Ulcer. Therapeutic advantage for omeprazole also has been documented in gastric ulcer. Comparative trials of omeprazole with ranitidine (80–82) or cimetidine (83) have shown higher healing rates for omeprazole.

A metaanalysis of trials comparing omeprazole 20 mg daily with either ranitidine or cimetidine in gastric ulceration is presented in Table 2. In the trials that compared omeprazole with ranitidine, 336 patients took omeprazole and 329 took raniti-

TABLE 2. METAANALYSIS OF COMPARATIVE STUDIES BETWEEN OMEPRAZOLE AND H_2-RECEPTOR ANTAGONISTS IN GASTRIC ULCER

	% healed (95% CI)			
	Four weeks		*Eight weeks*	
	Omeprazole	*Ranitidine*	*Omeprazole*	*Ranitidine*
Omeprazole 20 mg daily vs ranitidine 300 mg daily (reference 80–82)	73.0 (68.2 – 77.8)	62.0 (56.8 – 67.2)	91.3 (87.8 – 94.8)	85.1 (80.7 – 89.5)
	difference = 11.0%** (95% CI = 3.9 – 18.1)		difference = 6.2%† (95% CI = 0.6 – 11.8)	
	Omeprazole	*Cimetidine*	*Omeprazole*	*Cimetidine*
Omeprazole 20 mg daily vs cimetidine 400 mg bid (reference 83)	73.0	58.0	84.0	75.0
	difference = 15.0%†		difference = 9.0%	

**$P < 0.01$ Mantel-Haenszel chi-squared test.
†$P < 0.05$.

dine. In the trial of omeprazole and cimetidine, the numbers of patients analyzed who received either drug were 102 and 87, respectively.

In one study of gastric ulcer associated with nonsteroidal antiinflammatory drugs, 85–92% of patients healed their ulcers after eight weeks on omeprazole 20–40 mg daily compared with 53% on ranitidine 150 mg bid (81). In that study, no differences in relapse rates were observed for up to six months after healing with omeprazole or ranitidine.

Omeprazole in Treatment of Refractory Peptic Ulcer. There is no unanimous definition of refractory peptic ulcer, but most descriptions include failure of ulcer healing following at least eight weeks of treatment with an H_2-receptor antagonist in full dose. Omeprazole has been found to be highly effective in healing those ulcers that are genuinely refractory to H_2-receptor antagonists (84, 85). In one study (84), 18 patients with peptic ulcers that had not healed on conventional therapy were treated with omeprazole 40 mg daily for eight weeks. All ulcers healed, usually within two weeks. With the introduction of omeprazole, the concept of "refractory" peptic ulceration may require reexamination.

Omeprazole in Gastroesophageal Reflux Disease (GERD). Omeprazole has been shown to heal all grades of esophagitis and to suppress symptoms to a greater degree than the H_2-receptor antagonists (86–89). A metaanalysis of trials comparing omeprazole with H_2-receptor antagonists in the treatment of GERD is presented in Table 3. In trials of omeprazole 20 mg daily versus ranitidine, the data in Table 3 are derived from 210 patients on omeprazole and 227 on ranitidine. In comparisons between omeprazole and cimetidine, the data in Table 3 represent 138 patients on omeprazole and 134 on cimetidine.

A recently completed long-term study compared omeprazole 20 mg once daily with ranitidine 150 mg

TABLE 3. METAANALYSIS OF COMPARATIVE STUDIES BETWEEN OMEPRAZOLE AND H_2-RECEPTOR ANTAGONISTS IN REFLUX ESOPHAGITIS

	% healed (95% CI)			
	Four weeks		*Eight weeks*	
	Omeprazole	*Ranitidine*	*Omeprazole*	*Ranitidine*
Omeprazole 20 mg daily vs ranitidine 150 mg bid (references 86–88)	74.8 (68.9 – 80.7)	44.5 (38.0 – 51.0)	89.8 (84.5 – 95.1)	57.5 (48.9 – 66.1)
	difference = 30.3%* (95% CI = 21.6 – 39.0)		difference = 32.3%* (95% CI = 22.4 – 42.4)	
	Omeprazole	*Cimetidine*	*Omeprazole*	*Cimetidine*
Omeprazole 20 mg daily vs cimetidine 400 mg bid (reference 89)	56.0	26.0	71.0	35.0
	difference = 30.0%*		difference = 36.0%*	

*$P < 0.001$ Mantel-Haenszel chi-squared test.

twice daily (90). After one year of treatment, 70% of those patients who were given omeprazole were in symptomatic and endoscopic remission compared with 10% of those given ranitidine. During the healing phase of the study, there had been a slight increase in basal gastrin levels in those given omeprazole. However, this remained stable during the remainder of the 12-month study.

Patients with GERD resistant to treatment with H_2-receptor antagonists have been treated with higher doses of omeprazole. In one such study comparing omeprazole 40 mg once daily with ranitidine 300 mg twice daily, the healing rates after four weeks were 63% and 17%, respectively (91). In addition, 86% of patients on omeprazole were symptom-free compared with 32% on ranitidine.

No data are yet available from studies in the United States regarding the ability of omeprazole to induce regression of esophageal columnar epithelium in patients with Barrett's esophagus. However, there has been a report of regression of Barrett's epithelium from Belgium (92). This is a potentially very important finding but will require detailed confirmation in prospective studies.

A recent study has shown that omeprazole reduces the frequency of recurrence of esophageal strictures in patients with GERD who had received previous esophageal dilatation (93).

Omeprazole in Zollinger-Ellison Syndrome. In clinical trials involving treatment of approximately 200 patients with Zollinger-Ellison syndrome for up to five years, gastric acid secretion has been controlled adequately, and this has been associated with marked improvement in, or abolition of, symptoms (49, 52). The drug has been well tolerated, even in high doses, and no histological changes in the gastric mucosa have been observed.

SUMMARY

The introduction of omeprazole into clinical practice is a new development in the treatment of acid-peptic disease. Its unique mode of action produces profound suppression of gastric acid secretion. This has resulted in accelerated healing of esophagitis and peptic ulcer and in improved alleviation of symptoms. It is particularly effective in healing ulcers refractory to H_2-receptor antagonists and in controlling excessive gastric acid secretion seen in Zollinger-Ellison syndrome.

Combined clinical experience with omeprazole in the United States, Europe, and elsewhere has, to date, demonstrated a good safety profile with a low incidence of adverse events. Prolonged acid inhibition induced by chronic dosing with omeprazole results in hypergastrinemia. In preclinical toxicology studies in the rat, this has produced hyperplasia of gastric ECL cells and carcinoid tumors composed of these cells. Similar changes have been observed in rats given high doses of ranitidine, which is known to have an excellent record of safety in man. To date, omeprazole also has a wide margin of clinical safety.

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