

## Progress with Proton Pump Inhibition

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Received May 11, 1992

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The proton pump, a  $H^+/K^+$ -ATPase located on the secretory canalicular membrane of the parietal cell, forms the final pathway for gastric acid secretion. Omeprazole is concentrated in the secretory canalculus, where it is converted to its active form, which binds covalently with the  $H^+/K^+$ -ATPase, thus inhibiting acid secretion arising from any stimulus.

Meta-analysis has defined the primary determinants for peptic ulcer healing as the degree of acid suppression, the duration of suppression over 24 hours, and the length of treatment. The longer duration of acid suppression with omeprazole, particularly during the day, when food is ingested and  $H_2$ -receptor antagonists are less effective, is reflected in the clinical superiority for symptom relief and ulcer healing and especially for the treatment of erosive esophagitis. Extensive clinical experience has proved omeprazole to be safe, and concerns over hypergastrinemia, ECL-cell hyperplasia, and carcinoid formation have not been substantiated in humans. Recent evidence has shown that omeprazole suppresses *Helicobacter pylori* and, in combination with antibiotics, can eradicate this organism in a substantial proportion of patients. This effect may result from enhancement of antibiotic bioavailability and optimizing host defense mechanisms.

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The gastric parietal cell is regulated by a complex interaction of neural, endocrine, and paracrine factors. These act on muscarinic M3, gastrin, and histamine  $H_2$  receptors, respectively. Ligand binding to all three receptors initiates a cascade involving the release of intracellular calcium, while the binding of histamine to the  $H_2$  receptor also activates adenylate cyclase, causing an increase in cellular cyclic AMP [1]. Transduction via these pathways results in activation of the "proton pump," a  $H^+/K^+$ -ATPase, which is active only at the secretory canalicular membrane of the parietal cell. Whereas blockade of the cholinergic, histamine, or gastrin receptors can modulate or reduce acid secretion, only inhibition of this  $H^+/K^+$ -ATPase, which is the final common pathway to acid secretion, can abolish the secretory response to all known secretagogues.

Omeprazole is the first of a new class of substituted benzimidazole compounds that can specifically block the parietal cell  $H^+/K^+$ -ATPase and thus inhibit gastric acid secretion.

Omeprazole is a lipophilic weak base. It is absorbed from the proximal small intestine, distributed throughout the body with a plasma half-life of about one hour, and concentrated in the parietal cells. Within the parietal cells, omeprazole is concentrated and trapped in the highly acidic compartment of the secretory canalculus. Here, it is converted to its active sulfenamide form, which binds covalently to the  $H^+/K^+$ -ATPase, inactivating the pump, and thus inhibiting acid secretion. From

its mechanism of action, one may see that omeprazole can only be trapped and converted in an actively secreting parietal cell. This fact may partly explain why morning dosing, when the parietal cells are secreting in response to meal stimulation, has a greater effect on intragastric acidity than evening dosing [2,3].

As omeprazole is acid-labile, it is formulated as enteric-coated granules dispensed in a gelatine capsule. The granules release at an alkaline pH, allowing absorption of intact omeprazole into the circulation. Peak plasma levels occur about three hours after an oral dose [4]. The plasma half-life is short, and the drug is undetectable by about 11 hours after dosing. As the active form of omeprazole binds covalently to the  $H^+/K^+$ -ATPase enzyme, the plasma drug levels at any one time do not correlate with the degree of acid inhibition, which can be detected for three to four days after a single dose. The initial degree of acid inhibition does, however, correlate with the area under the plasma concentration time curve, which represents the amount of drug available to the parietal cells [5]. The bioavailability of omeprazole increases with repeated dosing, from 35 percent after a single dose to 60 percent after one week's administration, possibly due to increased absorption secondary to reduced intragastric acidity [2,6].

Omeprazole dose-dependently inhibits basal and stimulated gastric acid secretion [7] and also lowers 24-hour acidity, omeprazole, 30 mg daily, for one week, resulting in a 97 percent reduction in median 24-hour intragastric acidity [8].

Lansoprazole is the second agent in the class of substituted benzimidazoles to be developed for clinical use. It has a mechanism of action similar to that of omeprazole and also produces a dose-dependent decrease in basal and pentagastrin stimulated acid output. The effect on stimulated acid output increases with repeated dosing, from 81 percent reduction on day 2 to 90 percent reduction on day 8 of dosing with 30 mg daily [9]. Basal and stimulated acid outputs return to pre-treatment levels one week after cessation of treatment.

Another substituted benzimidazole, pantoprazole, which also profoundly reduced gastric acid secretion, has been withdrawn from further development due to toxicology problems.

All of these drugs bind covalently to the  $H^+/K^+$ -ATPase and thus act in a non-competitive manner. A new agent, a semi-naphthoquinone, derived from *Streptomyces aculeolatus*, acts competitively on the proton pump to inhibit acid secretion [10]. Development of this compound may lead to a new class of reversible proton pump inhibitors available for clinical use.

#### APPROPRIATE LEVELS OF ACID SUPPRESSION

Acid is considered central to the pathophysiology of duodenal and gastric ulcer and reflux esophagitis, and Schwartz's dictum, "no acid—no ulcer," still holds true.

Meta-analysis allows pooling of the results of clinical trials to assess the significance of any relationship or trend that might not be evident from any single smaller study. Predetermined criteria of eligibility, which have to be met in order for a study to be included in the pooling, are established. Such methods have been used to determine the degree of acid inhibition necessary for the optimal healing of acid peptic disorders. Initial analysis of various doses of  $H_2$ -receptor antagonists showed a clear linear relationship between nocturnal acid suppression and duodenal ulcer healing [11]. This finding reflects the predominant effect of these drugs on basal nighttime acid secretion. When omeprazole, which extends the period of acid

suppression into the daytime, was added to the analysis, healing was better correlated to suppression of 24-hour intragastric acidity.

A further extensive analysis of raw pH data from 490 individual patients utilized polynomial regression and response surface methodology [12]. This process defined the three primary determinants for duodenal ulcer healing to be the degree of acid suppression, the duration of suppression over the 24-hour period, and the length of treatment. Suppression to increase the intragastric pH to above 3.0 was not, however, found to increase ulcer healing further. Additional benefit was obtained by extending the duration of antisecretory effect or increasing the length of treatment. This model predicts 100 percent healing of duodenal ulcers at four weeks if the intragastric pH can be maintained at or above 3.0 for 18 hours of the 24. A similar approach has been applied to gastric ulcer [13,14], and the same three variables predict gastric ulcer healing, although the length of treatment is a more important variable than that for duodenal ulcer healing.

The healing of erosive esophagitis at eight weeks also correlates with the duration in hours that the intragastric pH is maintained above 4.0 ( $r = 0.87$ ;  $p < 0.05$ ) [15]. A close association also exists between healing at eight weeks and the reduction in esophageal acid exposure ( $r = 0.83$ ). This fact is not surprising, since there is a close relationship between the duration of suppression of intragastric acidity to above pH 4.0 and the reduction in esophageal acid exposure. We have constructed a model for reflux esophagitis using polynomial regression similar to that performed for duodenal and gastric ulcers [16]. Stepwise regression shows that the same three determinants of duration and degree of acid suppression and length of treatment are of approximately equal importance; however, the intragastric pH threshold above which further suppression has minimal effect on healing rates appears to be 4.0. Maintaining the intragastric pH at or above this threshold for 21 hours of each 24 predicts 100 percent healing of esophagitis at eight weeks.

Conventional doses of H<sub>2</sub>-receptor antagonists act best at suppressing basal acid output and exert most effect during the nighttime period of prolonged unstimulated acid secretion. They cannot overcome the integrated stimulus to acid production resulting from a meal, and this difficulty limits their duration of action [17,18]. Proton pump inhibition effectively blocks the acid secretory response to all stimuli and thus maintains a raised intragastric pH for prolonged periods throughout the full 24 hours (Fig. 1).

### THERAPEUTIC EFFICACY

The long duration of acid inhibition achieved by omeprazole translates into more rapid symptom relief and healing than is obtained with other therapeutic agents. A meta-analysis of pain relief in studies comparing omeprazole and ranitidine for the treatment of duodenal ulcer showed that 71 percent of patients treated with omeprazole, 20 mg daily, had complete relief of symptoms within two weeks, compared with only 58 percent of patients being symptom-free on treatment with ranitidine, 300 mg at night [19]. This result confirmed a significant therapeutic gain in favor of omeprazole. Omeprazole was as effective as ranitidine in the relief of nocturnal pain but was significantly more effective in relieving daytime pain ( $p < 0.001$ ). A similar advantage in favor of omeprazole was noted for gastric ulcer (65 percent of patients being pain-free on omeprazole, 20 mg, at two weeks, compared with 56 percent on ranitidine, 150 mg twice daily) and reflux esophagitis

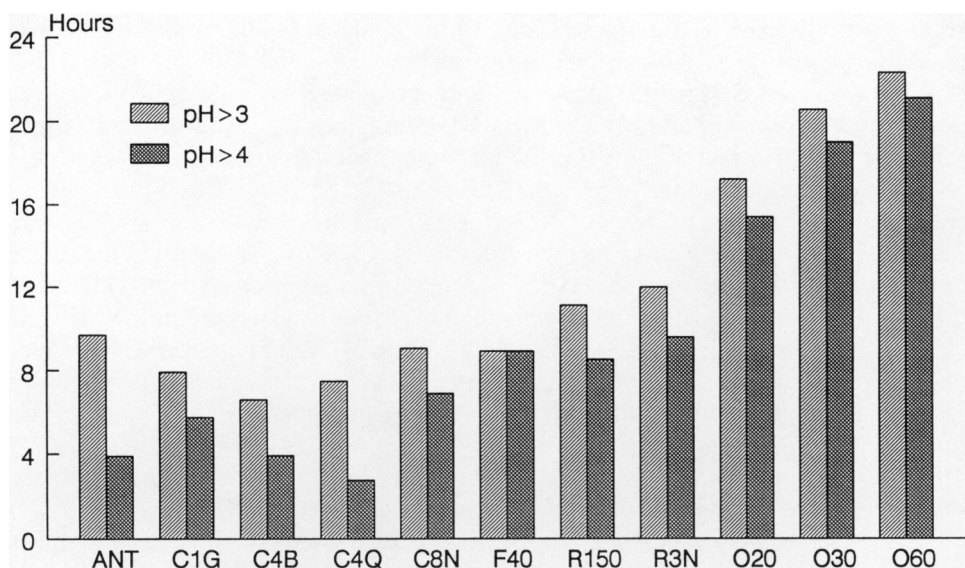


FIG. 1. Duration (hours) of the total 24-hour day that the intragastric pH is raised above the thresholds of pH 3 and 4 required for optimal healing of acid peptic diseases. ANT, antacid, 150 mmol, seven times a day; C1G, cimetidine, 200 mg, three times a day, and 400 mg at bedtime; C4B, cimetidine, 400 mg, twice a day; C4Q, cimetidine, 400 mg, four times a day; C8N, cimetidine, 800 mg, at bedtime; F40, famotidine, 40 mg, at bedtime; R150, ranitidine, 150 mg, twice a day; R3N, ranitidine, 300 mg, at bedtime; O20, omeprazole, 20 mg, once a day; O30, omeprazole, 30 mg, once a day; O40, omeprazole, 40 mg, once a day.

(64 percent of omeprazole-treated patients achieving relief of symptoms at four weeks, compared with 31 percent of ranitidine-treated patients) [19].

Omeprazole also produces more rapid healing of duodenal ulcers than ranitidine. Omeprazole, 20 mg daily, gives a two-week healing rate of 69 percent, compared with 53 percent for ranitidine, 300 mg daily [19]. The healing rates at four weeks were 93 percent for omeprazole and 83 percent for ranitidine. These differences were significant at both time periods ( $p < 0.001$ ). A similar therapeutic advantage is observed for omeprazole when compared with other drugs commonly used to treat duodenal ulcer, including sucralfate, colloidal bismuth, prostaglandin analogs, and the newer H<sub>2</sub>-receptor antagonists, nizatidine and famotidine [20]. The new proton pump inhibitor, lansoprazole, has also been shown to result in faster healing than H<sub>2</sub>-receptor antagonists. In comparative studies with ranitidine, lansoprazole, 30 mg, healed 93–95 percent of duodenal ulcer patients in four weeks, compared with 82–89 percent healing in those taking ranitidine, 300 mg, at night [21,22]. In a trial with famotidine, two-week healing rates of 54 percent were achieved with lansoprazole, 30 mg, compared with 39 percent of patients taking famotidine, 40 mg, at night. The healing rates at four weeks were 91 percent and 83 percent, respectively [23].

Omeprazole is also superior to H<sub>2</sub>-receptor antagonists for the treatment of gastric ulcer, although healing takes longer than for duodenal ulcer [19]. Healing rates of 73 percent at four weeks are obtained with omeprazole, 20 mg daily, increasing to 91 percent at eight weeks. In comparison, ranitidine, 150 mg twice daily, healed 62 percent at four weeks and 85 percent at eight weeks ( $p < 0.01$ ).

The leftward shift of the healing time curve noted with omeprazole is particularly

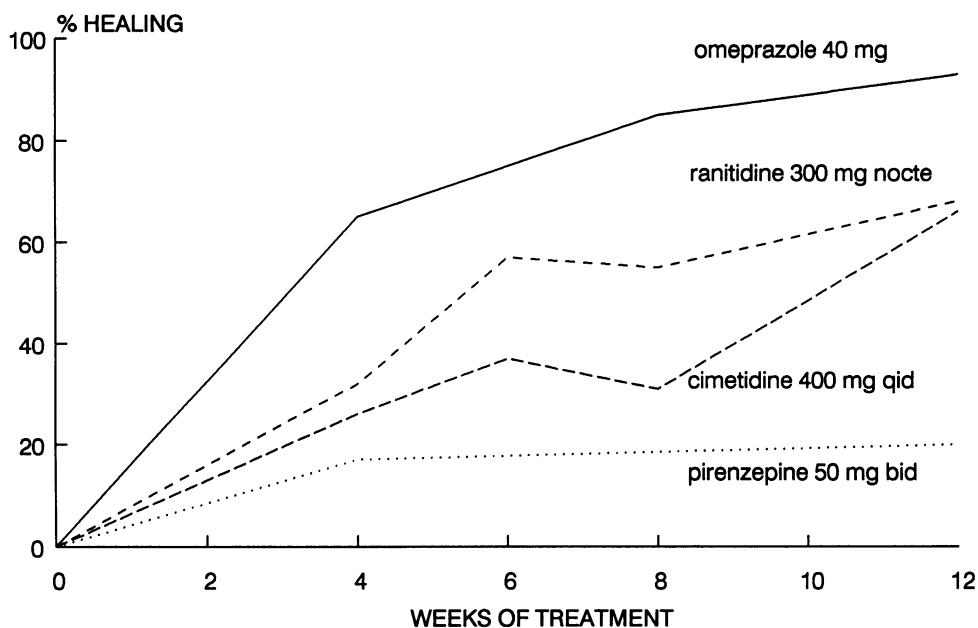


FIG. 2. Rate of healing of erosive esophagitis according to class of agent used.

evident in reflux esophagitis (Fig. 2). In comparative trials, omeprazole in doses of 20–60 mg healed 67–92 percent of patients with erosive esophagitis within four weeks. Ranitidine, 300 mg at night, healed only 27–45 percent of patients in the same time period [19,24]. Better healing rates are achieved with lower grades of esophagitis; 90–100 percent of patients with grade I–II disease healing within four weeks' treatment with omeprazole, compared with 53–55 percent of those treated with ranitidine. More severe grades of esophagitis also heal with omeprazole but require a longer time, 70 percent of those with grade III disease healing in four weeks and 90 percent at eight to 12 weeks. Even grade IV esophagitis responds to omeprazole treatment, 48 percent healing rates being seen at four weeks, rising to 62 percent at eight weeks [25]. Lansoprazole has also been shown to be superior to ranitidine in the short-term treatment of erosive esophagitis [26]. Once healed, omeprazole, 20 mg, is effective in preventing relapse of esophagitis, with 89 percent remaining in remission at 12 months, compared with 25 percent of those taking ranitidine, 150 mg twice daily [27].

#### CLINICAL SAFETY

More than 19,000 patients have been studied in clinical trials of omeprazole, the majority in comparative trials with ranitidine, and over 25 million patient treatments given worldwide. The incidence of adverse events reported by patients taking omeprazole is low and of a similar spectrum and severity to those patients receiving ranitidine or placebo [28]. Indeed, the incidence of severe adverse events in these trials was 1.1 percent compared to 4 percent among those taking placebo, and none of the serious adverse events was considered attributable to omeprazole. There is no increase in adverse events in elderly patients compared to those under 65 years of age, and omeprazole is safe in patients with renal or hepatic insufficiency. Extensive

post-marketing surveillance and data from the compassionate use program, in which patients have now been studied for up to seven years, have not revealed any significant adverse effects.

Concerns have been raised about the rise in plasma gastrin levels seen with omeprazole treatment and the potential for the development of ECL-cell carcinoid formation. Female rats treated over a lifetime with very high doses of omeprazole in toxicology studies show an increased incidence of gastric ECL-cell hyperplasia and carcinoid tumors [29]. Similar findings have been reported with short- and long-acting H<sub>2</sub>-receptor antagonists such as ranitidine and loxidine, the hypolipidemic compound ciprofibrate, and after partial gastric corpectomy [30–32]. This effect appears to be related to the hypergastrinemia associated with acid suppression achieved by a variety of means rather than a direct effect of any specific drug or class of drug.

Omeprazole treatment does produce a rise in plasma gastrin in man, related to the degree of acid suppression [33]. This effect is similar in extent to the rise in gastrin occurring after proximal gastric vagotomy and is approximately sixfold less than that seen in patients with pernicious anemia [34]. Furthermore, the plasma gastrin does not continue to rise with long-term treatment but plateaus out at approximately four times normal levels after four months' treatment with omeprazole, 40 mg daily [35]. No further rise was observed even after five years' treatment. No dysplasia of the gastric enterochromaffin-like cells occurred during the five years of follow-up. In another study of 122 patients treated with long-term omeprazole, gastric biopsies were studied to evaluate any possible changes in gastric endocrine cells [36]. Hyperplasia of a simple, linear, and/or micronodular type was noted in 11–19 percent of patients, but no dysplasia or neoplastic changes were seen. The mild changes of hyperplasia appeared to be related to interstitial or subatrophic gastritis and probably arise independently from omeprazole treatment [36].

ECL-cell changes similar to those observed in rats have not been seen in man despite extensive investigation, and omeprazole appears safe for short- and long-term use.

#### PROTON PUMP INHIBITION AND *HELICOBACTER PYLORI*

Epidemiological evidence suggests a close association between infection with *Helicobacter pylori* and peptic ulcer disease. A causal link has been proven with chronic active gastritis, but a similar role in the etiology of duodenal ulcer disease has not yet been confirmed [37]. The healing of duodenal ulcers is not dependent upon eradication of the organism nor is the ability to maintain remission with antisecretory therapy. Ulcer relapse rates are greatly reduced, however, by eradication of *H. pylori* and may even approach zero [37–39].

In clinical trials, omeprazole achieves temporary suppression of *H. pylori* in 50–90 percent of cases but fails to eradicate the organism [40–45]; however, the combination of omeprazole with amoxicillin, in doses of 750–2,000 mg per day, improves the eradication rate variably to about 30 percent with omeprazole, 20 mg, and 60–82 percent with omeprazole, 40 mg daily [46–51].

The mechanism of effect of omeprazole on *H. pylori* is uncertain. *In vitro*, both lansoprazole and omeprazole show direct toxicity against the organism with minimum inhibitory concentrations (MICs) similar to that of bismuth [52–54]. Lansoprazole is four times more potent than omeprazole in killing *H. pylori in vitro*. In

comparison, none of the H<sub>2</sub>-receptor antagonists tested showed any significant activity [54]. It is not known what concentration of omeprazole exists in the mucus layer and at the mucus layer-epithelial cell interface where *H. pylori* is found. Although rapidly converted in an acid environment, parent drug could conceivably be found in the mucus layer, due to the alkalinizing action of *H. pylori* urease, or under conditions of low acidity resulting from inhibition of acid secretion. This theory might explain the apparent redistribution of the organism during omeprazole treatment away from the gastric antrum, which might be at a relatively neutral pH toward the corpus, which is the site of acid production [45]. Interestingly, two acid-converted forms of lansoprazole are also bactericidal to *H. pylori in vitro*, with potencies two to four times that of lansoprazole alone [54].

Omeprazole might act simply by its effect on gastric acid secretion. Whether this effect would alter the bioavailability of antibiotics is unknown. The peak systemic concentrations achieved after oral dosing with amoxicillin and bacampicillin are reduced with omeprazole treatment, although the areas under the plasma concentration curves are unaltered [55]. Whether this effect might increase the local antibiotic bioavailability in the gastric lumen and mucus layer is unknown.

It has been suggested that increasing the intragastric pH might lead to overgrowth of competitive bacteria such as is seen in pernicious anemia, which is associated with a very low prevalence of *H. pylori*. It is, however, uncommon for omeprazole to cause complete anacidity throughout the 24 hours, and gastric juice is bactericidal below pH 4.0 within ten minutes [56]. A further hypothesis proposes that elevation of the pH removes the neutralizing action of acid on local ammonia produced by bacterial urease. This process results in bacterial "suicide from overalkalinization."

Clearly, larger controlled trials to investigate the action of proton pump inhibition with and without antibiotic co-therapy as a cure for duodenal ulcer disease are urgently required.

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