Omeprazole: Inhibiting the final common pathway to acid secretion - The acid pump

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ABSTRACT: Omeprazole is the first agent in a new therapeutic advance class – the proton or acid pump inhibitors – which represents a significant therapeutic advance in the treatment of acid related diseases. Omeprazole reduces gastric acid secretion at its source – the acid pump of the parietal cell, thereby offering precise and consistent clinical effects. Omeprazole once daily has been shown to heal over 80% of duodenal ulcers within two weeks and over 95% within four weeks. In gastric ulcer, the healing rates are up to 80% within four weeks and 96% within eight weeks. More patients are free from symptoms earlier on omeprazole therapy than with the H_2 receptor antagonists. Omeprazole is also effective in healing and symptom relief even where prolonged H_2 receptor antagonist therapy has been unsuccessful. Omeprazole has been shown in clinical trials to be the first consistently effective treatment of erosive/ulcerative reflux esophagitis. Complete healing is achieved in the majority of patients and symptom relief is rapid. In clinical trials with 20 mg once daily, over 70% of patients healed within four weeks and up to 85% healed within eight weeks. Also, patients with erosive/ulcerative reflux esophagitis resistant to three months or more of treatment with full therapeutic doses of H_2 receptor antagonists have shown significant benefit, with healing rates of 49% within four weeks and 73% within eight weeks of therapy with omeprazole. The rare Zollinger-Ellison syndrome has been difficult to treat in the past due to the massive hypersecretion of gastric acid. Omeprazole has proved highly effective in this syndrome, being well tolerated by patients who have received more than five years of continuous treatment with daily oral doses up to 160 mg. In summary, in extensive clinical trials omeprazole has been shown to be highly effective in the treatment of duodenal and gastric ulcers, erosive/ulcerative reflux esophagitis and Zollinger-Ellison syndrome. Omeprazole is well tolerated and is without any established side effects when used for short periods. It remains to be established whether H_2 blockers still represent the best available therapy for acute treatment of peptic disorders, and whether maintenance therapy is best achieved with H_2 blockers or with proton pump blockers. **Can J Gastroenterol 1989;3(2):61-71** *(Pour résumé, voir page 62)*

Key Words: *Acid pump, Duodenal ulcers, Gastric ulcers, Omeprazole*

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THE KEY TO THE PRECISE CONTROL of acid related diseases lies in an understanding of the proton pump of the parietal cell (1). Gastric acid is secreted by the proton pump of the parietal cell located in the oxyntic glands of the gastric mucosa. A large concentration gradient of hydrogen ions is established across the secretory membrane in the parietal cell and this results in a substantial difference in pH between the cytosol of the parietal cell (pH 7.4) and the lumen of the secretory canalicula (approximately pH 1). The parietal cell has an extensive system of secretory canaliculi and tubulovesicles and is specialized for acid secretion. The tubulovesicles fuse with the membranes of the secretory canaliculi to form an enlarged secretory surface when the parietal cell is stimulated.

Hydrogen ions are secreted across the surface by the proton pump and are exchanged for potassium ions. This pump is an enzyme, H^+,K^+-ATPase, that exchanges hydrogen ions from the cytosol of the parietal cell with potassium ions from the secretory canaliculi. This exchange is preceded by the passive movement of hydrogen ions and chloride ions out of the cell cytoplasm into the secretory canaliculi upon stimulation of the parietal cell. The net effect is that hydrochloric acid is formed in the secretory canaliculi. Thus, this enzyme, H^+,K^+-ATPase, the final common pathway for

L'omeprazole: Inhibiteur de la voie commune finale de la sécretion acide — La pompe à acide

RESUME: L'omeprazole est le premier agent d'un nouvelle classe de substances thérapeutiques avancées — les inhibiteurs de la pompe à acide ou à proton — qui représentent un progrès important dans le traitement des affections associés à l'acide gastrique. L'omeprazole réduit la sécretion d'acide gastrique à la source — la pompe à acide de la cellule pariétale gastrique à la source — la pompe à acide de la cellule pariétale, procurant ainsi des effets cliniques précis et consistants. Administré une fois par jour, l'omeprazole a fait ses preuves en guérissant 80% des ulcères duodénaux en moins de deux semaines et plus de 95%, en moins de quatre semaines. Dans le cas des ulcères gastriques, les pourcentages de guérison sont de 80% en moins de quatre semaines et de 96% en moins de huit semaines. Traités à l'omeprazole, un nombre plus élevé de patients deviennent asymptomatiques plus rapidement qu'avec les antagonistes du récepteur H_2. L'omeprazole s'avère également efficace dans la guérison et le soulagement des symptômes, même après que le traitement prolongé aux antagonistes du récepteur H_2 a échoué. D'après les études cliniques, l'omeprazole est le premier traitement de l'esophagite à reflux gastroesophagien corrosif/ulcératif dont l'efficacité est consistante. La guérison totale est obtenue pour la majorité des patients et le soulagement des symptômes est rapide. Au cours d'études cliniques où 20 mg ont été administrés une fois par jour, plus de 70% des sujets ont été guéris en quatre semaines ou moins, et le pourcentage atteint 85% en l'espace de huit semaines. Les patients atteints d'esophagite à reflux corrosif/ulcératif, jusque-là résistants à un traitement de trois mois et plus aux antagonistes du récepteur H_2 administrés à pleine dose, ont eu aussi montré des résultats significatifs avec 49% de guérisons en moins de quatre semaines et 73% en huit semaines de traitement à l'omeprazole. Par le passé, l'hypersécrétion d'acide gastrique rendait le syndrome de Zollinger-Ellison difficile à soigner. L'omeprazole a prouvé sa pleine efficacité dans le traitement de ce syndrome et le médicament est bien toléré par les patients ayant suivi un traitement continu pendant plus de 5 ans avec une dose quotidienne orale atteignant 160 mg. En résumé, au cours d'études cliniques approfondies, l'omeprazole a démontré sa grande efficacité dans le traitement du syndrome de Zollinger-Ellison, de l'esophagite à reflux corrosif/ulcératif, et de l'ulcère gastrique et duodenal. Utilisé sur de courtes périods, l'omeprazole est bien toléré et ne semble pas produire d'effets secondaires établis. Il reste encore à déterminer si les antagonistes du récepteur H_2 représentent toujours la meilleure thérapie pour le traitement des affections peptiques, et si ce sont eux ou les inhibiteurs de la pompe à proton qui conviennent le mieux à la thérapie d'entretien.

acid secretion, is known as the proton or acid pump. Evidence from monoclonal antibody studies suggests that this enzyme is specific to the parietal cell (2).

The phases of acid production include cephalic, gastric, intestinal and interdigestive stages. The cephalic phase is activated by way of the vagal nerve; the gastric phase is stimulated by peptides, amino acids and gastrin; the intestinal phase is influenced by absorbed amino acids; and the interdigestive phase is influenced by vagal nerves, mast cells and histamine. The parietal cell is stimulated to secrete acid by activation of receptors on its basolateral membrane (3). Following activation of the histamine, gastrin or acetylcholine receptors, intracellular second messengers (such as cyclic AMP and calcium) transmit the stimulus to the secretory membrane of the parietal cell where acid secretion begins (4). Additional activators include factors such as epidermal growth factor, somatostatin and prostaglandins. The acetylcholine receptor is calcium dependent but the gastrin receptor appears to be calcium independent.

Gastrin released in response to food stimulates gastric acid secretion by the parietal cell. When the acid concentration in the stomach is high and the intragastric pH is low, gastrin secretion falls and further acid secretion is prevented. Thus, the gastrin mechanism is a naturally occurring feedback system which operates in response to variations in intragastric luminal pH.

WHAT IS OMEPRAZOLE?

The binding of omeprazole to H^+,K^+-ATPase, the proton pump, is activated in the acidic environment of the enzyme in the parietal cell. Omeprazole influences acid secretion at the final common pathway rather than at the surface receptor or at the intracellular cyclic AMP, protein kinase or calcium level. Omeprazole is a sulphoxide compound containing two ring structures, pyridine and benzimidazole (Figure 1A). This lipophilic compound of molecular weight 345.42 penetrates membranes rapidly, is a weak base (owing to the presence of the pyridine ring) and is activated in the acidic environment of the parietal cell close to the target enzyme, the proton pump. The oral formulation is supplied in hard gelatin capsules containing enteric coated granules. The capsule dissolves in the stomach, but the enteric coating ensures that omeprazole is protected until it reaches the small intestine where it is absorbed. An intravenous formulation is available, supplied as a vial and an ampoule.

Omeprazole shows H^+,K^+-ATPase inhibitory activity below pH 4, with omeprazole gaining protons; this 'protonated' omeprazole is transformed into the active inhibitor of the proton pump, a sulphenamide (Figure 1B). The sulphenamide reacts with a mercapto (SH) group of the H^+,K^+-ATPase, which is accessible from the luminal side of the secretory canalicular membrane. A disulphide (-SS-) link is formed between the active inhibitor and the enzyme (5) and this inactivates the enzyme (6).

ANIMAL STUDIES

The acute toxicity of omeprazole in animals is low: the LD_{50} (the lethal dose in 50% of the animals tested) for acute oral administration in mice and rats cannot be obtained with precision, since the highest dosage that could be given practically (4 g/kg) did not cause death in either species (7). The highest intravenous dose (50 mg/kg) that could be given in the rat was also nonlethal. In mice, the acute intravenous LD_{50} was estimated to be 82.8 mg/kg, the dosage at the top of the range that could be physically given.

The gastrin response to acid inhibi-

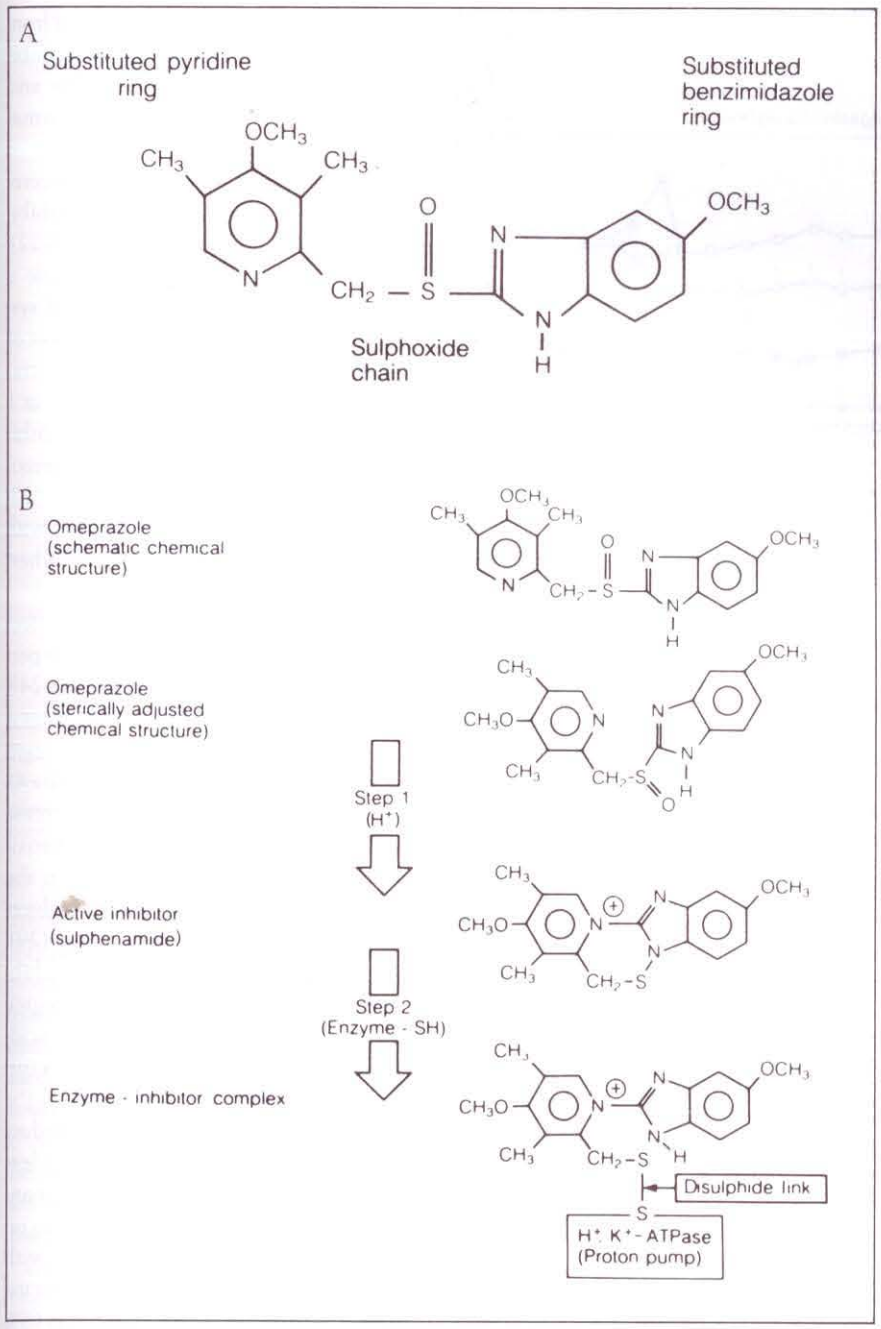

Figure 1) A *Omeprazole consists of three parts, all of which are essential for its biological action, a substituted pyridine ring, a substituted benzimidazole ring and a connecting sulphoxide containing chain.* **B** *In the acidic secretory canaliculi of the parietal cell close to the proton pump, omeprazole gains protons and this 'protonated' omeprazole is rapidly transformed into a sulphenamide, the active inhibitor of the proton pump. The sulphenamide reacts rapidly with a mercapto (-SH) group of the H+,K+-ATPase, which is accessible from the luminal side of the secretory canalicular membrane. A disulphide (-SS-) link is formed between the active inhibitor and the enzyme and this effectively inactivates the enzyme (56)*

tion is a normal physiological event: when gastric acid secretion is inhibited, the intragastric pH rises and there is a feedback increase in the release of gastrin from the antral G cells of the stomach. Thus, the greater the acid inhibition, the greater the rise in gastrin. In long term toxicology studies of omeprazole in the rat (7,8), a dose dependent and reversible hypertrophy of the gastric mucosa was reported, including gastric enterochromaffin-like (ECL) cell hyperplasia secondary to profound and long standing acid inhibition. It is of note that in short and long term clinical use of omeprazole, no changes in mucosal histology have been reported.

In a two year toxicity study in the rat, gastric ECL cell hyperplasia and carcinoids were found (7). ECL cells are the dominant endocrine cell type in the rat gastric mucosa and gastric ECL cell carcinoids were found in some animals (8), developing towards the end of the animal's natural life span. The earliest occurrence of a carcinoid was after 19 months of continuous and profound acid inhibition for almost the entire natural lifetime of the animal. This ECL cell hyperplasia/carcinoids was found to be due to hypergastrinemia, the natural feedback response to profound acid inhibition. The proliferation was not a direct effect of omeprazole. Such proliferation is also seen following the administration of the gastrin analogue pentagastrin and also experimentally following surgical exclusion of the antrum (9). High dose ranitidine also causes hypergastrinemia and has been shown to increase gastric ECL cell density in female rats (10).

What is the relevance of these studies to man? Gastric carcinoids are rare in man (11,12) and are relatively benign and slow growing (13,14). Gastric ECL cell carcinoids have been associated with atrophy of the gastric body with or without pernicious anemia (13,15,16) and with the Zollinger-Ellison syndrome (17). The dependence of gastric carcinoids on the trophic stimulation of gastrin is supported by the fact that gastric carcinoids have not been reported after Billroth I and II gastric resections (which involves the removal of the antral gastrin containing G cells), and that partial gastrectomy with antrectomy in patients with nonantral atrophic gastritis has resulted in regression of gastric carcinoids (18,19).

HUMAN PHARMACOLOGY

The pharmacological effects of omeprazole have been extensively studied in healthy subjects and in duodenal ulcer patients in remission. Acid inhibition with omeprazole 20 mg once daily, inhibits acid secretion over 24 h. This effect is rapid in onset, dose dependent and increases during the first few days of treatment after which time it stabilizes. Acid control is maintained in chronic use and

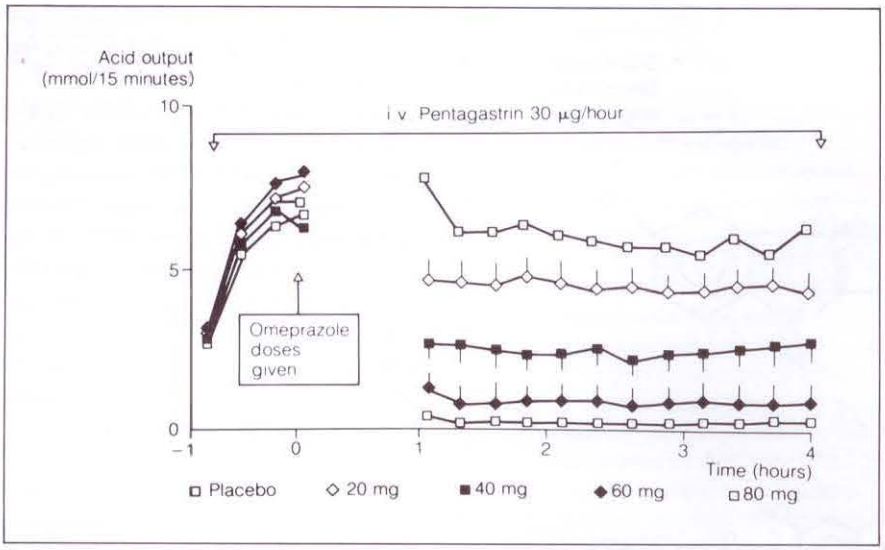

Figure 2) *Stimulated acid secretion was achieved in six healthy volunteers by the administration of intravenous pentagastrin, and oral omeprazole was given in doses of 20 to 80 mg (20). Omeprazole showed a dose dependent inhibition of acid secretion: A single 20 mg dose reduced mean stimulated acid output by 36% 1 to 4 h after administration*

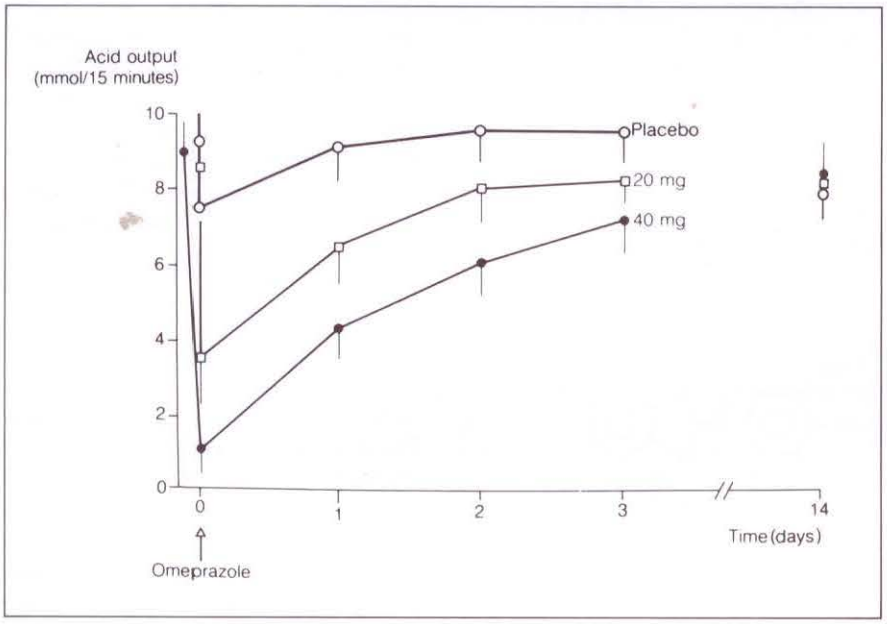

Figure 3) *The omeprazole induced inhibition of acid secretion is reversible, and after a single dose of omeprazole, acid inhibition returns to normal in two to three days (20)*

acid secretion smoothly returns to normal within three to four days of stopping omeprazole treatment. Omeprazole causes a dose dependent inhibition of pentagastrin stimulated acid secretion in healthy subjects (Figure 2). There is a rapid increase and then decline in the plasma concentration of omeprazole (half-life 40 mins) after a single oral 20 or 40 mg dose (20). The peak plasma concentration of omeprazole is reached after 1 to 3 h when it is given as the enteric coated formulation.

The degree of acid inhibition is correlated to the area under the plasma omeprazole concentration-time curve and the given dose of omeprazole. However, the degree of acid inhibition at any given point in time is not correlated with the plasma concentration at that point in time, since the duration of acid control is long, inhibiting acid secretion long after the plasma levels of the drug are undetectable. Thus, once daily omeprazole provides effective acid inhibition during a 24 h period, even though omeprazole or its metabolites have disappeared from the blood. Omeprazole induced inhibition of acid secretion is reversible and after a single dose returns to normal within two to three days (Figure 3).

With repeated dosing, the antisecretory effect of this proton pump inhibitor increases and then stabilizes (20-22). This increasing effect of omeprazole is thought to be due to an enhanced systemic availability and long duration of action (23). With repeated administration of enteric coated omeprazole at a dose of 20 mg once daily, the mean inhibition of peak acid output is approximately 60% in healthy volunteers (22, 24,26) and about 70% in patients with duodenal ulcer disease (27,28) when measured 24 h after dosing.

Another method to assess the effect of a drug on intragastric acidity is to perform repeated measurements over a 24 h period. After repeated dosing with varying doses of omeprazole, acid secretion is inhibited dose dependently (Figure 4), with 20 mg giving an average decrease in 24 h intragastric acidity of approximately 80%. Omeprazole taken in the morning or in the early evening produces similar control of acid secretion (29). Duodenal ulcer healing with acid inhibitors is best correlated with the degree of suppression of 24 h intragastric acidity (rather than suppression of nocturnal acidity) (30).

It is important to know that the reduction in 24 h intragastric acidity is less using standard doses of H_2 receptor antagonists (31-33). For example, mean reduction in 24 h intragastric acidity with cimetidine 200 mg bid has been reported to be 55%, ranitidine 150 mg bid is 69% and famotidine 40 mg nocte is 70%.

Fasting plasma gastrin concentrations remains normal until there is greater than an 80% inhibition of stimulated acid output after omeprazole. There was little or no change 24 h after a single dose (34). The disease induced hypergastrinemia in patients with Zollinger-Ellison syndrome has not been altered by up to 120 mg of omeprazole during five years of therapy (35,36). In patients with ranitidine resistant peptic ulcer and reflux esophagitis who received omeprazole at a dose of 40 mg daily, the basal plasma gastrin concentration increased a further

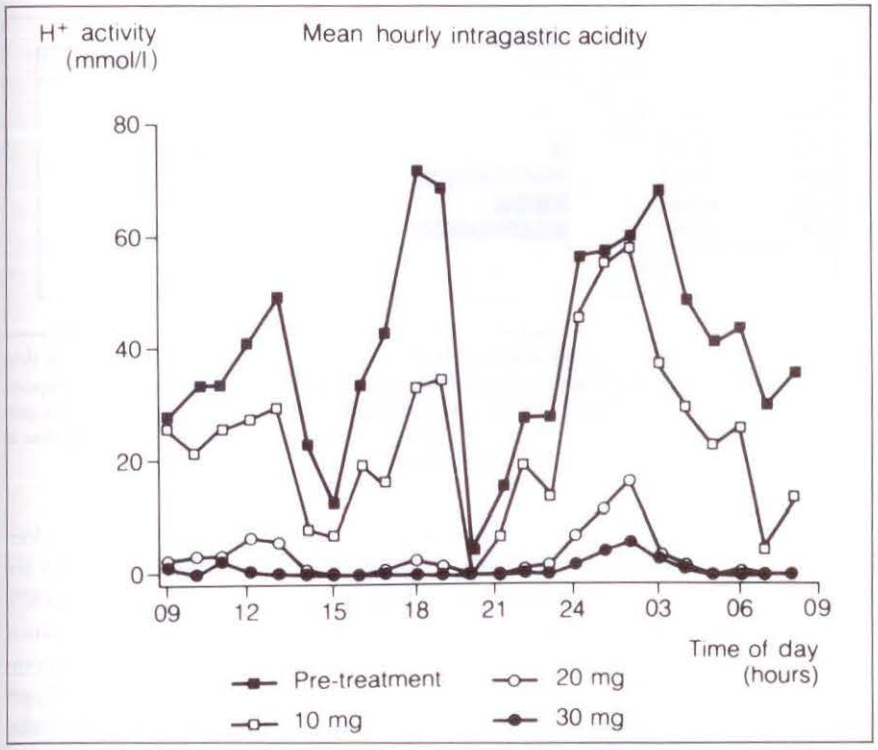

Figure 4) *Twenty-four hour intragastric acidity is reduced in duodenal ulcer patients in remission after dosing with omeprazole for seven days (53). After seven days of omeprazole there is an 80% reduction of 24 h intragastric acidity. The same control is achieved whether omeprazole is given in the morning or in the early evening (29)*

89 pg/mL and then remained unchanged for periods of up to four years (37). Repeat endoscopic biopsies in these patients have demonstrated no treatment related histological abnormalities. The small reduction in pentagastrin stimulated pepsin output observed with high doses of omeprazole (20,38) is likely due to the reduced volume of secretion from the oxyntic glands. Intrinsic factor secretion is unchanged after single or repeated dosing with omeprazole (39).

Omeprazole has no effect on plasma concentrations of somatostatin, insulin or glucagon and the slight decline in the postprandial levels of secretin is an expected result of the reduced acid load on the duodenum following gastric acid inhibition (40,41). Omeprazole has no effect on plasma levels of C-peptide, parathyroid hormones, thyroid hormones, sex hormones such as prolactin, testosterone or estradiol, or basal levels of cortisol (20,22,41-45). Gastric emptying rate is unchanged after a single dose of omeprazole (46) and the lower esophageal sphincter pressure is unaffected (47). The increases in concentration of viable bacteria, nitrite and N-nitroso compounds observed in 10 subjects given omeprazole, 30 mg daily for two weeks (48) are not thought to be of clinical significance (49). Thus, gastric carcinoma certainly will not develop with short term use of omeprazole, but viable bacteria, nitrite and N-nitroso compounds are seen after omeprazole therapy, and if this is prolonged for several years, the possibility of development of gastric cancer is enhanced.

Absorption of omeprazole from enteric coated formulation in a gelatin capsule occurs in the small intestine usually within 3 to 6 h. Peak plasma concentrations are reached within 1 to 3 h of a single dose and absorption of omeprazole is unaffected by intake of food or antacids. The small volume of distribution of omeprazole (0.3 to 0.4 L/kg) (50) corresponds to the volume of the extracellular fluid. Omeprazole is 95% bound to plasma protein and is extensively metabolized on first pass through the liver. The systemic bioavailability of a single dose of omeprazole (20 mg enteric coated) is 35% compared with the same dose administered intravenously. This bioavailability increases to approximately 60% after repeated, once daily administration (50-52).

The bioavailability of omeprazole in duodenal ulcer patients is similar to that in young, healthy volunteers (53-55). This may increase to 79% of a single oral 20 mg dose when given in buffered solution to elderly individuals (56), possibly as a result of the age related decrease in first pass metabolism of omeprazole. Bioavailability may increase slightly to 70% in patients with impaired renal function (57). In patients with chronic cirrhosis of the liver, omeprazole has a bioavailability of approximately 98% due to impaired hepatic first pass metabolism effects (58). The plasma clearance differs between individuals, possibly due to variations in liver bloodflow and the degree of first pass metabolism (50). Despite the relatively short plasma half-life of omeprazole in man (about 40 mins) (59) once daily dosing leads to acid control over a 24 h interval. This duration of action of omeprazole far exceeds the short plasma half-life of omeprazole, likely due to the prolonged inhibition of action of the proton pump.

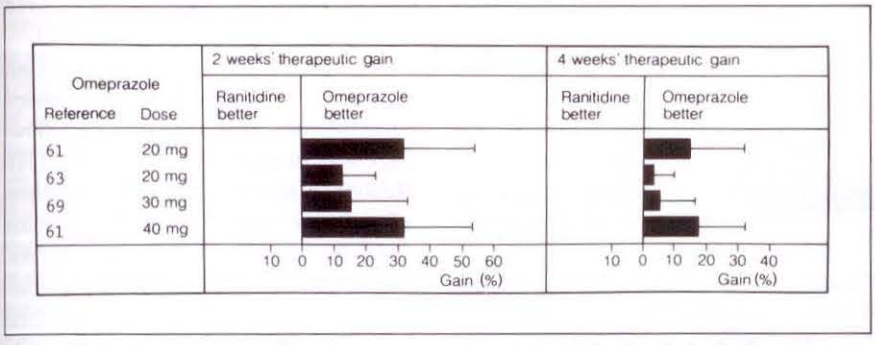

Figure 5) *In all comparative studies of omeprazole and ranitidine in duodenal ulcer healing (61,68,69), there was a 'therapeutic gain' of omeprazole at two and four weeks. The therapeutic gain represents the percentage difference (absolute) in healing rate between omeprazole and ranitidine with 95% confidence intervals*

CLINICAL STUDIES

Duodenal ulcer: Over 2000 patients have participated in clinical trials examining the therapeutic benefits of using omeprazole in duodenal ulcer. In dose ranging, double-blind studies evaluating the effects of omeprazole in doses from 10 to 60 mg once daily in a total of 405 patients (60,61), the 20 mg daily dose was found to be highly effective, with a mean of 78% of ulcers healing within two weeks and mean of 97% healing within four weeks. Daily doses of 30 to 60 mg were found to be similarly effective. A loading dose has been found to have no influence on duodenal ulcer healing with omeprazole (62).

Therapeutic gains in healing have been achieved with omeprazole in comparison with H_2 receptor antagonists (Figure 5). Double-blind comparisons of omeprazole with H_2 receptor antagonists in duodenal ulcer have included over 1400 patients. The comparison drugs were cimetidine in five trials and ranitidine in three trials (61,63-69). Consistently higher healing rates were obtained in omeprazole treated patients than those treated with cimetidine in the comparative trials, both at two weeks and at four weeks. At two weeks the healing rate for patients who received omeprazole, 20 to 40 mg daily, was in the range 58 to 82%. The corresponding figures for those receiving standard doses of cimetidine were 44 to 49%. At four weeks the figures were 84 to 100% for omeprazole and 74 to 84% for cimetidine. Omeprazole 20 to 40 mg once daily also produced higher healing rates than ranitidine, 150 mg bid, both at two weeks and at four weeks. Omeprazole healed 71 to 83% of duodenal ulcers after two weeks and 92 to 100% of ulcers after four weeks. Ranitidine healed 53 to 60% after two weeks and 82 to 91% after four weeks. The recommended standard dose, 20 mg, of omeprazole produced significantly higher healing rates than standard dose ranitidine (61).

Large duodenal ulcers usually take longer to heal than small ones, but 52% of ulcers greater than 10 mm diameter are healed at two weeks with omeprazole versus 35% with H_2 antagonists (61,63-65,68). Healing rates with omeprazole in smokers are superior to healing rates

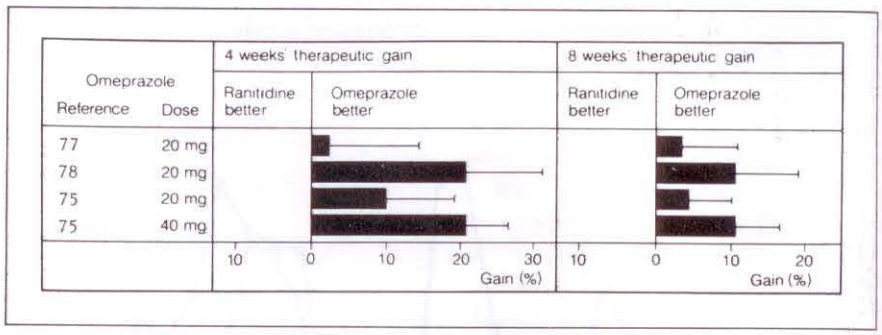

Figure 6) *Omeprazole 20 mg once daily has been compared with ranitidine 150 mg bid in three studies (75,77,78). Omeprazole healed more ulcers more quickly at weeks 4 and 8, showing a 'therapeutic gain' in healing ranging from 2 to 21% at four weeks and from 3 to 11% at eight weeks. Therapeutic gain represents the absolute percentage difference in healing rate between omeprazole and ranitidine in patients with gastric ulcer, with 95% confidence limits*

in patients receiving H_2 receptor antagonists and the patient's age, sex and alcohol consumption has not been found to be influential on ulcer healing rates with omeprazole. The speed and degree of symptom relief with omeprazole is superior to that achieved with cimetidine and ranitidine (61,62,70-72). For example, in comparison with ranitidine, omeprazole treated patients experienced fewer days of pain (median one to two days) than ranitidine treated patients (median seven days). However, both drugs provide rapid and effective relief of nocturnal pain (61).

Duodenal ulcer patients healed with omeprazole have been followed-up in periods ranging from six to 12 months (28,60-63,73). In the first six months after healing, without further treatment, 34% of patients developed symptomatic ulceration. No difference in relapse rates was detected in patients originally healed after two weeks' therapy compared with those healed after four weeks' therapy (73). In a 12 month follow-up study, the incidence of ulcer relapse was 56% (60). Symptomatic ulcer recurrence in the first six months after healing with omeprazole occurred in 48% of such individuals as compared with 60% of patients healed with cimetidine (63), a difference which was not statistically significant. Six-month relapse rates following healing with ranitidine or omeprazole were comparable (61).

Gastric ulcer: Omeprazole has shown therapeutic gains over cimetidine and ranitidine, both in terms of healing rate and symptom relief in clinical trials involving approximately 1200 patients with gastric ulcers. Healing in gastric ulcer is generally slower than in duodenal ulcer. Four and eight week healing rates are higher with 40 mg versus 20 mg (80% versus 69% at four weeks and 96% versus 89% at eight weeks, respectively) compared to ranitidine (59% and 85%, respectively) (74). Healing rates were also higher with omeprazole than with cimetidine in prepyloric gastric ulcer (75). Studies comparing gastric ulcer healing with omeprazole 20 mg versus ranitidine 150 mg bid showed that ulcers healed more quickly with omeprazole than with ranitidine, showing a therapeutic gain ranging from 2 to 21% at four weeks and 3 to 11% at eight weeks (Figure 6). Omeprazole healing rates at eight weeks were similar in smokers and nonsmokers and healing rates were unaffected by age, sex and alcohol consumption.

The healing rate with omeprazole 20 and 40 mg daily, was substantially higher than with ranitidine 150 mg bid in patients with gastric ulcer receiving NSAIDs (74). There is a statistically significant difference in favour of omeprazole in relief of daytime pain compared with ranitidine (Figure 7) (74,76,77).

Six month untreated follow-up data in gastric ulcer patients has demonstrated no difference in recurrence rate following either omeprazole or ranitidine (74).

Resistant ulcers: A small proportion of patients treated with H_2 receptor antagonists will fail to heal their ulcers. In patients with endoscopically confirmed duodenal, gastric or anastomotic ulcer unhealed after long term therapy with H_2 receptor antagonists, omeprazole was found to be very effective: duodenal ulcer patients had been treated for

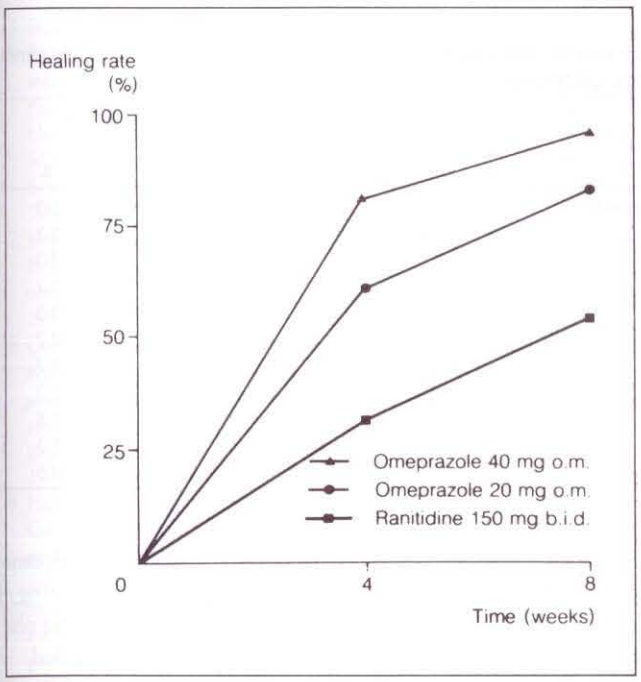

Figure 7) *In a comparative trial of patients with nonsteroidal anti-inflammatory drug associated gastric erosion and ulceration (75), the four week healing rates were higher for omeprazole 20 to 40 mg once daily than for ranitidine 150 mg bid*

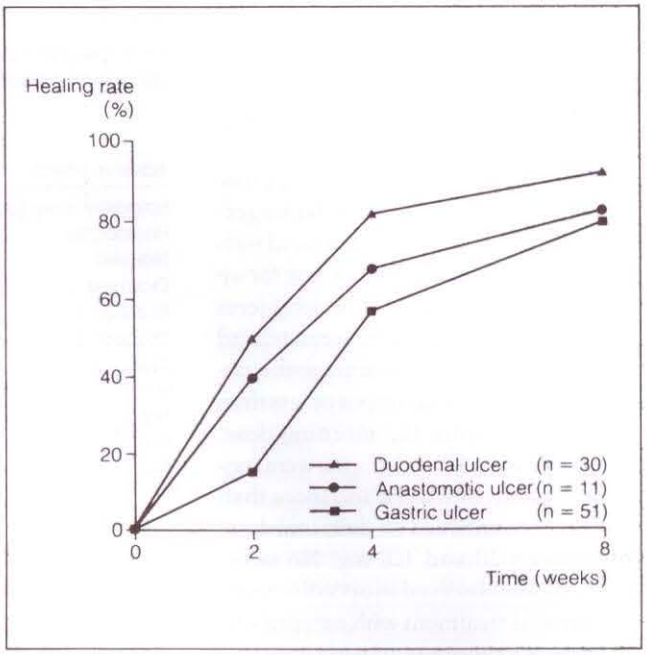

Figure 8) *The effect of omeprazole on resistant ulcers was examined (79). After treating patients with cimetidine or ranitidine for a mean of 32 weeks for duodenal ulcer, 29 weeks for gastric ulcer and 46 weeks for anastomotic ulcer, oral omeprazole 40 mg once daily was given for two to eight weeks. Over 80% of the ulcers then healed within eight weeks*

an average of 32 weeks with H_2 receptor antagonists; those with gastric ulcer had been treated for a mean of 29 weeks; and those with anastomic ulcer had been treated for a mean of 46 weeks with either cimetidine or ranitidine. Oral omeprazole 40 mg once daily was given for two to eight weeks and approximately 80% of the duodenal ulcers healed in four weeks as did gastric ulcers; anastomotic ulcers healed after eight weeks of omeprazole therapy (Figure 8) (78).

Reflux esophagitis: Symptomatic relief and endoscopically confirmed complete healing of reflux esophagitis has been found to be effective with omeprazole. Omeprazole has been compared with ranitidine in three double-blind studies in erosive/ulcerative reflux esophagitis (79-81). Omeprazole was given in doses of 20, 40 or 60 mg daily and ranitidine given in the standard daily dose of 150 mg bid. In these studies omeprazole produced significantly better healing rates than ranitidine, both at four weeks and at eight weeks, with about twice as many patients healed with omeprazole as with ranitidine (Figure 9). At four weeks the healing rates were 67% with omeprazole 20 mg once daily versus 31% for ranitidine 150 mg bid, whereas at eight weeks the healing rates were 85% and 50%, respectively (80). Those patients still unhealed after eight weeks of ranitidine were then switched to omeprazole and 13 of these 15 patients (87%) were healed after eight weeks of omeprazole, whereas only one of three patients unhealed after eight weeks of omeprazole therapy was healed after a further eight weeks of ranitidine therapy. The highest healing rates with omeprazole were seen in mild cases and any healing benefits of omeprazole over ranitidine were most pronounced in those patients with severe disease (80-82), with healing rates unaffected by age, sex, smoking or alcohol. After a four week course of treatment, a significantly larger proportion of omeprazole treated patients (80%) were free from heartburn compared with those on ranitidine (30%) (79-81). Overall, symptom relief was more rapid and more pronounced with omeprazole than with ranitidine (80), with 65% of omeprazole treated patients being symptom-free after two weeks, compared with 25% of ranitidine treated patients.

In patients with reflux esophagitis unhealed after at least three months of treatment with at least 1200 mg of cime-

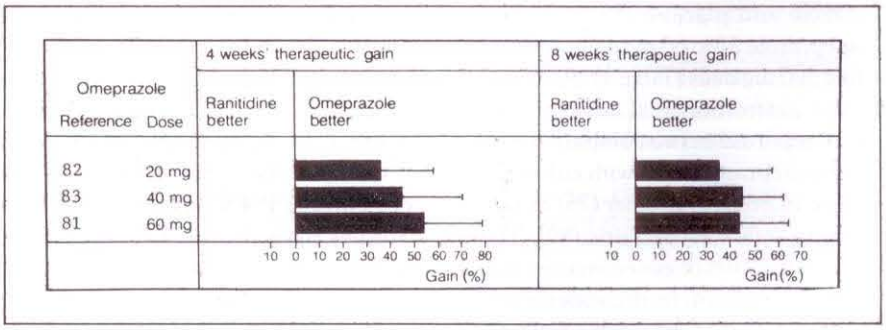

Figure 9) *Three double-blind studies have compared omeprazole with ranitidine in erosive/ulcerative reflux esophagitis (80-82). Oral omeprazole was given at 20, 40 or 60 mg daily and ranitidine was given at 150 mg bid. For the three doses of omeprazole, a 'therapeutic gain' in healing was observed at weeks 4 and 8. Therapeutic gain represents the absolute percentage difference in healing rate between omeprazole and ranitidine with 95% confidence limits*

tidine daily, or at least 300 mg of ranitidine daily, 49% were healed after four weeks of omeprazole 40 mg daily, 73% after eight weeks and 81% after 12 weeks (83).

Zollinger-Ellison syndrome: Approximately 200 patients with Zollinger-Ellison syndrome have been treated with omeprazole in clinical trials, some for up to five years (35,36,42). The long term mean daily dose varied between 60 and 70 mg daily in order to achieve the target reduction in acid output of less than 10 mmol/h before the morning dose. Approximately 80% of patients were controlled within one week and more than 90% were maintained on daily oral doses of between 20 and 120 mg. No tachyphylaxis was observed in up to five years' continuous treatment with omeprazole. There was a pronounced early improvement in acid related symptoms, with the therapy being well tolerated and no treatment related mucosal abnormalities found on histological evaluation of biopsy samples (36,84).

SAFETY

A lack of systemic side effects of omeprazole is perhaps to be expected since the drug targets precisely the acid pump. Furthermore, it is biologically inactive at the physiological pH prevailing in tissues and organs other than the secretory canaliculi of the parietal cell. Nonserious, mild and transient adverse events which have been reported most often are gastrointestinal in nature and include epigastric pain, nausea, diarrhea, constipation, flatulence, headache and a few cases of skin rash. No difference in adverse events could be detected between omeprazole and placebo (85) or between omeprazole 20 to 60 mg daily and ranitidine 300 mg daily (Table 1). Significantly fewer gastrointestinal adverse events were reported in two comparative trials with omeprazole than with either cimetidine in prepyloric ulcer (75) or ranitidine in reflux esophagitis (80). There were no reports of gynecomastia, impotence, confusion in the elderly or increases in serum creatinine concentration with omeprazole. The pooled incidence of serious adverse events has been similar in comparative trials for omeprazole, cimetidine and ranitidine, and less than the incidence of serious adverse events during placebo therapy (4.7%), probably resulting from the untreated disease.

TABLE 1

Most frequent adverse events reported in clinical trials of omeprazole versus ranitidine in duodenal ulcer, gastric ulcer and reflux exophagitis

	Omeprazole		Ranitidine	
Adverse effect	Number of patients	%	Number of patients	%
Epigastric pain (aggravated)	59	5.7	39	5.0
Headache	33	3.2	18	2.3
Nausea	29	2.8	24	3.0
Diarrhea	28	2.7	13	1.7
Flatulence	28	2.7	18	2.3
Dyspepsia	25	2.4	33	4.2
Abdominal pain	24	2.3	13	1.7
Vomiting	18	1.7	18	2.3
Fatigue, asthenia	12	1.2	14	1.8
Dizziness	10	1.0	10	1.3
Skin rash/urticaria	5	0.5	4	0.5

No histological changes in oxyntic endocrine cells of the gastric mucosa have been found after short term healing courses of omeprazole or H_2 receptor antagonists in peptic ulcer disease patients (84-86,87). No treatment related histological abnormalities of these cells have been found in up to five years of continuous high dose omeprazole therapy in patients with Zollinger-Ellison syndrome (86,88). Once daily oral omeprazole at a dose of 40 mg daily has been without histological sequelae over the past three years, in a trial still in progress, in peptic ulcer and reflux esophagitis patients resistant to cimetidine or ranitidine and treated with omeprazole (90). Omeprazole has not been shown to have any significant clinical effect on laboratory variables (85), and provocation testing in subjects in whom an increase in the liver enzymes aspartate and alanine aminotransferases and alkaline phosphatase have been reported, have not confirmed a further and subsequent change in those individuals (91,92).

Omeprazole is metabolized by the cytochrome P-450 system in the liver. Studies have shown that omeprazole does not interfere with the pharmacokinetics of oral or intravenous theophylline or oral propranolol (93,94) but interactions with diazepam (95,96) and phenytoin (95,97) have been described. Small changes in the low potency R-isomer of warfarin but not with the potent S-isomer have been described with omeprazole 20 mg daily (98). Monitoring of omeprazole patients also receiving phenytoin or warfarin is recommended.

SUMMARY

In extensive clincial trials omeprazole has been shown to be highly effective in the treatment of duodenal and gastric ulcers, reflux esophagitis and Zollinger-Ellison syndrome, with fast and pronounced symptom relief both during the day and at night. Omeprazole has been well tolerated and has been without any established side effects. Time and experience will be needed to establish whether H_2 blockers still represent the best available therapy for acute treatment of peptic disorders and whether maintenance therapy is best achieved with H_2 blockers or with proton pump blockers.

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