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Omeprazole
A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Peptic Ulcer Disease and Zollinger-Ellison Syndrome

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Summary

Synopsis: *Omeprazole[1] is a substituted benzimidazole derivative which markedly inhibits basal and stimulated gastric acid secretion. It has a unique mode of action, irreversibly blocking the so-called proton pump of the parietal cell which is supposedly the terminal step in the acid secretory pathway.*

In animals, on a weight basis, omeprazole is 2 to 10 times more potent than cimetidine in inhibiting gastric acid secretion. Toxicological studies in rats have shown that very high doses of omeprazole administered for 2 years produce hyperplasia of gastric enterochromaffin-like cells and carcinoids, a few with proliferations into the submucosa. The significance of such findings to the clinical situation is wholly speculative and requires further research. Preliminary studies in patients with duodenal ulcers or Zollinger-Ellison syndrome have found no mucosal changes which would suggest that the drug represents a risk for development of carcinoid tumours at therapeutic dosages.

In patients with duodenal ulcers omeprazole, at dosages of at least 20mg once daily, produced ulcer healing rates of between 60 and 100% after 2 weeks and between 90 and 100% after 4 weeks, even in patients resistant to treatment with H_2-receptor antagonists. Comparative trials clearly demonstrated that omeprazole 20 to 40mg administered once daily was significantly more effective than usual dosage regimens of cimetidine and ranitidine in healing duodenal ulcers during 2 to 4 weeks of treatment. At present no data are available evaluating omeprazole as maintenance therapy once ulcers have healed. Other clinical trials have also shown that omeprazole is effective for treating gastric ulcers, ulcerative peptic oesophagitis, and Zollinger-Ellison syndrome. In patients with Zollinger-Ellison syndrome the profound and long lasting antisecretory activity of omeprazole may make it the drug of choice for treating the massive acid hypersecretion associated with the disease, especially when H_2-receptor antagonists are ineffective. During clinical trials

1 'Losec', 'Lozec', 'Losek' (AB Hässle, Astra; not yet commercially available).

reported to date omeprazole has been very well tolerated but further clinical experience is essential to fully evaluate its safety profile.

Thus, omeprazole represents a pharmacologically unique antisecretory drug which is very effective for rapidly healing peptic ulcers and peptic oesophagitis, and for reducing gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. If the apparent absence of undesirable mucosal morphological changes during treatment with usual doses in patients with peptic ulcer disease is confirmed, it may be a major advance in the treatment of these diseases.

Pharmacodynamic Studies: *In vitro* and *in vivo* animal studies demonstrated that omeprazole produces long lasting inhibition of gastric acid secretion which is likely due to non-competitive binding of a proton-activated derivative to parietal cell (H^+/K^+)-ATPase. Such a mechanism, at the terminal stage of the acid secreting process, means a reduction of intragastric acidity can now be achieved independent of the nature of the primary stimulus. Comparative studies in animals found omeprazole to be some 2 to 10 times more potent than cimetidine on a weight basis.

Single-dose studies in man (healthy volunteers and patients with duodenal ulcer disease or Zollinger-Ellison syndrome) have shown that omeprazole inhibits both basal and stimulated gastric acid secretion in a dose-dependent manner. Following repeat once daily administration, omeprazole has an increasing effect on acid secretion which appears to stabilise after about 3 days. Short term studies indicate that 20 to 30mg once daily is the optimum dosage regimen in healthy volunteers and patients with duodenal ulcer disease in remission; this virtually abolishes gastric acidity within 6 hours and reduces stimulated acid output after 24 hours by 60 to 70%.

In addition to its effects on gastric acidity, omeprazole reduces the total volume of gastric juice secreted and inhibits pepsin output. However, these changes are not as consistent or as great as the effect on acid secretion. Omeprazole 0.35 mg/kg administered intravenously did not significantly affect basal or stimulated intrinsic factor secretion. Furthermore, omeprazole does not seem to have any significant influence on gastric emptying rate, or on the majority of gastrointestinal hormones – apart from gastrin. Short periods of treatment with omeprazole administered once daily usually resulted in elevated serum gastrin levels. Such hypergastrinaemia occurs secondary to a pronounced reduction of intragastric acidity, and returns to normal levels within 1 to 2 weeks of stopping treatment.

Orally, but not parenterally, administered omeprazole seems to be cytoprotective in some animal models of peptic ulcer disease such as Shay ulcers, stress-induced ulcers, and ulcers induced by various necrotising agents. The mechanisms involved are not fully understood but appear to be independent of the established antisecretory properties of omeprazole.

Toxicological studies in rats have demonstrated that supramaximal doses of omeprazole administered for long periods cause gastric enterochromaffin-like cell hyperplasia and carcinoids, a few with proliferations into the submucosa. It has been suggested that hypergastrinaemia, induced by the profound inhibition of gastric secretion causes these changes; their relevance to the therapeutic use of omeprazole remains speculative and further studies are required.

Pharmacokinetic Studies: The absorption characteristics of omeprazole are both formulation- and dose-dependent. Following administration of the drug as a buffered oral solution, buffered encapsulated uncoated granules, or as capsules of enteric-coated granules, mean peak plasma omeprazole concentrations were attained after 20 minutes, 30 minutes, and between 2 and 5 hours, respectively. Interestingly, increased doses of omeprazole produced disproportionately larger increases in mean peak plasma concentration and systemic availability. Similarly, repeat once daily administration for 5 to 7 days resulted in significant elevations of mean peak plasma concentration and area under the plasma concentration-time curve. Since omeprazole is acid labile, these findings could

possibly indicate that the antisecretagogue improves its own absorption and relative bioavailability by inhibiting acid secretion. An alternative explanation involves saturation of enzymes responsible for the first-pass metabolism of omeprazole.

Following intravenous administration omeprazole plasma concentrations decline biexponentially. The apparent volume of distribution of omeprazole is about 0.3 to 0.4 L/kg which is compatible with localisation of the drug in extracellular water. Penetration of omeprazole into red blood cells is low, whereas its plasma protein binding is high – between 95 and 96% in human plasma.

Omeprazole is eliminated rapidly and almost completely by metabolism; no unchanged drug has been recovered in the urine. Following absorption, 3 metabolites of omeprazole have been identified: a sulphone derivative, a sulphide derivative and hydroxyomeprazole. Peak plasma concentrations of the sulphone metabolite are attained shortly after those of unchanged omeprazole, 0.4 to 1.7 hours after peak omeprazole concentrations following administration of capsules of enteric-coated granules. However, unidentified metabolites of omeprazole had a very similar plasma concentration-time curve as the parent drug – in terms of peak concentration and the time to achieve it. Following administration of ^{14}C-omeprazole approximately 60% of total radioactivity is recovered in the urine within 6 hours. Over a 4-day period about 80% of the administered dose was recovered in the urine and the remainder in the faeces. Total plasma clearance is relatively high (32 to 40 L/h) and most studies have reported a mean elimination half-life of omeprazole in healthy subjects of between 0.5 and 1.5 hours (usually about 1 hour).

There are limited data available concerning the pharmacokinetic properties of omeprazole in patients with peptic ulcer disease or Zollinger-Ellison syndrome.

The pharmacokinetic profile of omeprazole does not seem to be altered in patients with chronic renal failure and is not influenced by haemodialysis.

Omeprazole plasma concentration does not correlate with its antisecretory activity at a given time-point; indeed, the drug markedly inhibits acid secretion long after plasma concentrations have decreased below detection limits. However, there does seem to be a significant correlation between antisecretory activity and area under the plasma concentration-time curve.

Therapeutic Trials: Clinical trials have demonstrated that omeprazole at dosages of at least 20mg once daily produces a duodenal ulcer healing rate of between 60 and 100% within 2 weeks and between 90 and 100% within 4 weeks. Dose-finding studies showed that an optimal dosage of omeprazole is between 20 and 40mg once daily. Open clinical studies have confirmed these very high rates of duodenal ulcer healing even in a small group of patients who were refractory to treatment with H_2-receptor antagonists (alone or in combination with other antiulcer drugs). Appropriately designed comparative clinical trials clearly demonstrated that once-daily administration of omeprazole 20 to 40mg produces significantly more rapid healing of duodenal ulcers after 2 to 4 weeks of treatment than the H_2-receptor antagonists cimetidine and ranitidine. Additionally, omeprazole 20mg and 40mg once daily elicited significantly greater symptom relief than ranitidine 150mg twice daily, whereas in 2 other studies 30mg and 20mg of omeprazole were indistinguishable from cimetidine 1000 mg/day and ranitidine 300 mg/day, respectively, in this respect. Other clinical studies have shown that omeprazole administered once daily may be effective for treating gastric ulcers and ulcerative peptic oesophagitis. Indeed, omeprazole 40mg once daily was significantly superior to ranitidine 150mg twice daily in 178 patients with reflux oesophagitis. Furthermore, in a double-blind multicentre trial in 184 outpatients with gastric ulceration, omeprazole 20mg once daily was as effective as ranitidine 150mg twice daily and healed 95% of gastric ulcers within 8 weeks.

In patients with Zollinger-Ellison syndrome, omeprazole is a highly potent and long acting antisecretagogue which many authors consider will become the drug of choice for controlling the massive acid hypersecretion associated with the disease. For patients with Zollinger-Ellison syndrome who are resistant to H_2-receptor antagonists, omeprazole of-

fers a valuable therapeutic alternative to surgery (partial or total gastrectomy) with its inherent risks.

Side Effects: Preliminary experience with omeprazole has found the antisecretagogue to be well-tolerated, producing no consistent side effects or changes in laboratory variables. Wider clinical usage with careful surveillance is needed to fully evaluate the side effect profile of omeprazole.

Dosage and Administration: The usual oral adult dosage of omeprazole seems to be 20mg once daily before breakfast for 2 to 4 weeks for duodenal ulcers and 4 to 8 weeks for gastric ulcers. In patients with Zollinger-Ellison syndrome omeprazole dosage should be individualised so that the smallest dose is administered which reduces gastric acid secretion to less than 10 mEq for the last hour before the next dose. At present, insufficient data are available for dosage recommendations in children.

1. Pharmacodynamic Studies

Omeprazole (fig. 1) is a substituted benzimidazole which markedly inhibits basal and stimulated gastric acid secretion in animals and man. It is the first of a new class of antiulcer drugs likely to be introduced into clinical practice (it is not yet commercially available) and is thought to reduce acid secretion by inhibiting hydrogen/potassium adenosine triphosphatase [(H^+/K^+)-ATPase], believed to be the proton pump of the parietal cell. This mechanism, at the terminal stage of the acid secreting process, means that for the first time intragastric acidity can be reduced independent of the nature of the primary stimulus. Since inhibition of gastric acid is a most important indicator of the therapeutic potential of drugs used to treat peptic ulceration, omeprazole might be expected to offer some advantages for the treatment of this disease. Independent of its clinical future, omeprazole is already an important pharmacological 'tool' for investigating physiological and biochemical changes that occur in the gastric mucosa and for evaluating the mechanisms of action of gastric acid inhibitors.

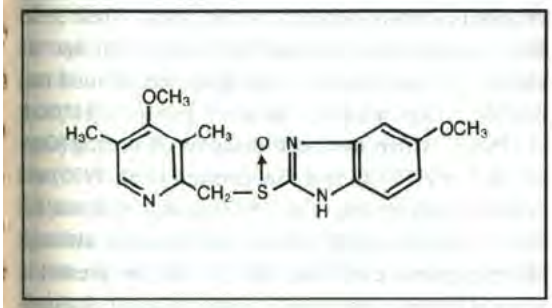

Fig. 1. Structural formula of omeprazole.

1.1 Site and Mechanism of Action of Omeprazole

Superficially, upper gastrointestinal ulceration has a relatively simple underlying aetiology which involves some loss of ability of the mucosa to protect against gastric acid and/or excessive secretion of acid. The complex morphological changes that occur with regard to mucosal cytoprotection in relation to the various conditions found in the upper gut are currently poorly understood and drug treatment has been largely devoted to controlling luminal acidity (Berglindh & Sachs 1985).

Hydrochloric acid, one major cause of upper gastrointestinal tract ulcers, is secreted from parietal (oxyntic) cells by the gastric proton pump [gastric (H^+/K^+)-ATPase], distal to cyclic adenosine monophosphate (cAMP), in response to at least 3 different types of stimulation – cholinergic (vagal), histaminergic and gastrinergic (Sachs 1984) [fig. 2]. It follows that an individual antagonist to any one of the 3 (or more) receptor types will only

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