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Clinical Pharmacology of Omeprazole

Colin W. Howden

University Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, Scotland

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Summary

Omeprazole is a specific inhibitor of H^+,K^+-ATPase or 'proton pump' in parietal cells. This enzyme is responsible for the final step in the process of acid secretion; omeprazole blocks acid secretion in response to all stimuli. Single doses produce dose-dependent inhibition with increasing effect over the first few days, reaching a maximum after about 5 days. Doses of omeprazole 20mg daily or greater are able to virtually abolish intragastric acidity in most individuals, although lower doses have a much more variable effect. Omeprazole causes a dose-dependent increase in gastrin levels.

Omeprazole must be protected from intragastric acid when given orally, and is therefore administered as encapsulated enteric-coated granules. Absorption can be erratic but is generally rapid, and initially the drug is widely distributed. It is highly protein-bound and extensively metabolised. Its elimination half-life is about 1h but its pharmacological effect lasts much longer, since it is preferentially concentrated in parietal cells where it forms a covalent linkage with H^+,K^+-ATPase, which it irreversibly inhibits. Omeprazole binds to hepatic cytochrome P450 and inhibits oxidative metabolism of some drugs, the most important being phenytoin.

Omeprazole has produced short term healing rates superior to the histamine H_2-receptor antagonists in duodenal ulcer, gastric ulcer and reflux oesophagitis. It has also been shown to be highly effective in healing ulcers which have failed to respond to H_2-receptor antagonists, and has been extremely valuable in treating patients with Zollinger-Ellison syndrome.

1. Chemistry and Pharmacology of Omeprazole

1.1 Chemistry

The molecular structure of omeprazole is composed of a substituted pyridine ring linked to a benzimidazole by a sulfoxide chain (fig. 1). Its molecular weight is 345 daltons. Omeprazole is a lipophilic weak base, and will therefore preferentially accumulate in an acidic environment such as the secretory membrane of the parietal cell.

1.2 Mode of Action

Omeprazole is avidly taken up by the parietal cell. In an acidic pH it becomes converted to its active form, a sulphenamide, by protonation. In this form, the drug produces an irreversible linkage via a disulfide bond with the enzyme H^+,K^+-ATPase or 'proton pump' (fig. 2) which is responsible for the active secretion of hydrogen ions by the parietal cells (Sachs & Wallmark 1989; Wallmark 1989) .

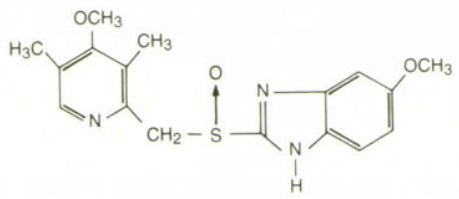

Fig. 1. Chemical structure of omeprazole.

This action makes omeprazole unique among existing gastric antisecretory drugs which are competitive antagonists at specific cellular receptors on the basolateral aspect of the parietal cell. Through its irreversible inhibition of H^+,K^+-ATPase, omeprazole blocks gastric acid secretion in response to all known stimuli including agents such as dibutryl cyclic adenosine monophosphate (db-cAMP), which acts intracellularly (Wolfe & Soll 1988).

Omeprazole is degraded by acid, and so must be protected from gastric acid when given orally; this is achieved by the use of encapsulated enteric-coated granules.

2. Pharmacodynamics in Humans

2.1 Effect on Basal Acid Output

Following oral administration of omeprazole in its encapsulated enteric-coated granule formulation, its maximal effect on gastric acid secretion is

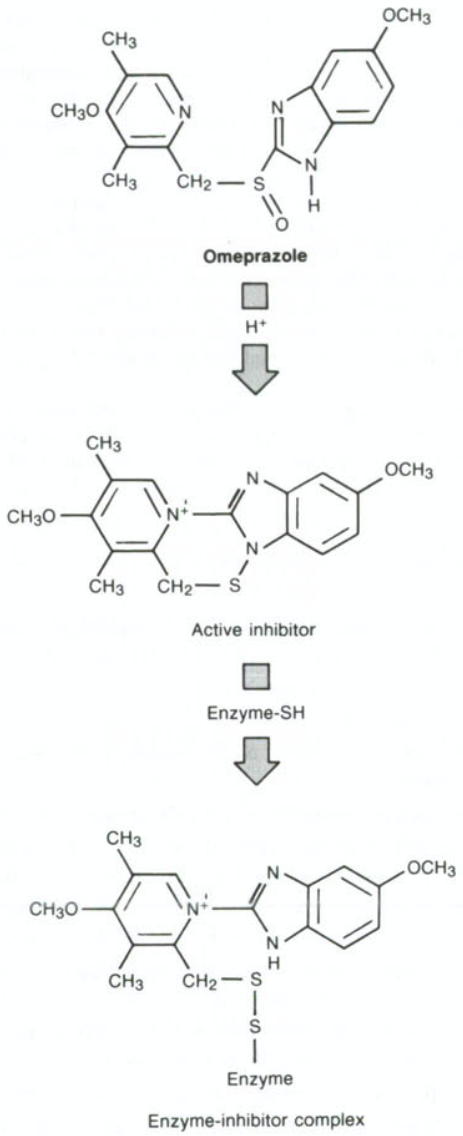

Fig. 2. Diagram of the interaction of the activated form of omeprazole with gastric H^+,K^+-ATPase.

achieved after about 6 hours: in a group of 6 healthy male subjects given omeprazole 30mg, basal acid output measured 6 hours later was reduced by 66% (Howden et al. 1984a). After 1 week of daily administration of the same dose, the inhibition of basal acid output had risen to almost 100%. In a similar group of 6 subjects given omeprazole 60mg daily, inhibition of basal acid output was 91.7% after the first dose and 99.1% after the seventh.

In a separate study, the effects of 7 days' administration of omeprazole 10mg daily were assessed (Howden et al. 1985a). A single dose of 10mg did not significantly affect basal acid output, but after 7 days of dosing mean basal acid output was reduced by 93%. However, there was a high degree of interindividual variability in response to this low dose.

These studies show a dose-dependent effect of omeprazole on inhibition of basal acid output. They also show variability in response to low dose omeprazole, and increased antisecretory effect with repeated dosing.

2.2 Effect on Pentagastrin-Stimulated Acid Output

Intravenous infusion of pentagastrin 1.2 μg/kg for 1 hour increased gastric acid secretion in a group of 6 healthy male subjects from a mean (± SD) basal value of 4.3 ± 3.4 mmol/h to a plateau value of 35.4 ± 5.4 mmol/h (Howden et al. 1984a). Omeprazole 30mg reduced the pentagastrin-stimulated plateau acid output to 10.2 ± 10.1 mmol/h (−71.2%; $p < 0.05$). After 7 days of dosing with omeprazole 30mg daily, this was further reduced to 0.6 ± 1.0 mmol/h (−98.4%; $p < 0.01$).

In subjects given omeprazole 60mg daily, pretreatment plateau acid output was 37.1 ± 10.6 mmol/h. After 1 dose this was reduced to 1.7 ± 2.3 mmol/h (−95.3%; $p < 0.01$); after the seventh dose, it was 0.4 ± 0.2 mmol/h (−99%; $p < 0.01$). In subjects given omeprazole 10mg daily (Howden et al. 1985a), pretreatment plateau acid output was 23.3 ± 8.2 mmol/h. Six hours after a single dose of 10mg, the figure was 23.1 ± 8.6 mmol/h (not significant) but at a similar time after the seventh daily dose it was 7.8 ± 6.7 mmol/h (−66.5%; $p < 0.01$). Again, there was a high degree of interindividual variability in response to the low dose.

In a group of patients with healed duodenal ulcer, pentagastrin-stimulated acid output after 7 days of dosing with placebo or omeprazole 5 or

10mg daily was measured 14 hours after the final dose (Howden et al. 1986a). Total output was 42.9 ± 4.9 mmol following placebo, and 34.5 ± 9.8 and 32.3 ± 8.7 following omeprazole 5 and 10mg, respectively. Neither of the reductions in output produced by these low doses of omeprazole was significant.

2.3 Effect on Insulin-Stimulated Acid Output

Omeprazole 30mg as a single oral dose reduced the stimulated acid output induced by an intravenous infusion of insulin 0.03 U/kg/h (Utley et al. 1985) from 16.8 ± 2.2 to 4.3 ± 1.8 mmol/h (−74%; $p < 0.05$). A similar group of subjects received a single dose of omeprazole 60mg, and in this group the insulin-stimulated acid output was reduced from 12.3 ± 2.6 to 3.4 ± 2.1 mmol/h (−73%; $p < 0.05$).

2.4 Effect on 24-Hour Intragastric Acidity

In a group of 9 patients with duodenal ulcer in clinical remission, a regimen of omeprazole 30mg daily for 1 week virtually eliminated intragastric acidity, with mean hourly hydrogen ion activity falling from 38.5 to 1.95 mmol/L (Walt et al. 1983). The median intragastric pH rose from 1.4 to 5.3, representing a much greater increase than that achieved by conventional doses of existing histamine H_2-receptor antagonists.

In another study, 12 duodenal ulcer patients received omeprazole 20mg daily for 28 days (Lanzon-Miller et al. 1987). At the end of that time, median integrated 24-hour intragastric acidity had fallen from 1148 to 36 mmol/L • h (−97%). The same patients also received a separate course of treatment with ranitidine 150mg twice daily; the median integrated 24-hour intragastric acidity with that treatment was 490 mmol/L • h (−57% compared with pretreatment values).

Omeprazole 20mg daily for 8 days reduced intragastric acidity by around 99% in 6 patients with healed duodenal ulcer (Naesdal et al. 1987) but had a much smaller effect on another 4 patients in the same study, indicating some degree of interindividual variability in response to this dose.

Finally, a dosage regimen of omeprazole 5 or 10mg daily for 7 days did not have any significant effect on 24-hour intragastric acidity in a group of 6 patients with healed duodenal ulcer (Howden et al. 1986a).

2.5 Effect on Plasma Gastrin Levels

Plasma concentrations of a wide variety of gastrointestinal peptides were measured in 6 healthy subjects 6 hours after a single oral dose of omeprazole 40mg (Allen et al. 1984). The basal level of gastrin was significantly ($p < 0.05$) increased from 13 ± 6.8 to 28.2 ± 8.3 pmol/L. The integrated gastrin response to a meal was also increased, but failed to reach statistical significance. No significant changes were found in the concentrations of any of the other peptides measured.

In a group of 12 healthy volunteers given omeprazole 40mg daily for 9 days by Festen et al. (1986), fasting serum gastrin levels increased from 36 ± 3 to 49 ± 6 ng/L ($p < 0.01$) after the first dose and to 59 ± 6 ng/L after the ninth ($p < 0.002$).

A nonsignificant increase in serum gastrin levels was found in 1 study of 10 duodenal ulcer patients given omeprazole 20mg daily for 8 days (Naesdal et al. 1987). Omeprazole 5 or 10mg daily for 7 days also produced no alteration in fasting gastrin levels in a group of 6 duodenal ulcer patients (Howden et al. 1986a). However, the median integrated gastrin response to a meal was significantly increased from 29.2 to 67.0 pmol/L • h ($p < 0.05$) following 7 days of omeprazole 10mg daily.

The median integrated 24-hour plasma gastrin was significantly raised from 328 to 1519 pmol/L • h in a group of 12 duodenal ulcer patients given omeprazole 20mg daily for 28 days (Lanzon-Miller et al. 1987). The median integrated 2-hour plasma gastrin for the same group of patients given ranitidine 150mg twice daily for 28 days was 799 pmol/L • h.

Omeprazole produces a dose-dependent increase in gastrin levels. The rise in integrated 24-hour gastrin is directly proportional to the reduc-

tion in integrated 24-hour intragastric acidity (Lanzon-Miller & Pounder, personal communication).

2.6 Effect on Pepsin Secretion

Although omeprazole has a dramatic effect on secretion of gastric acid, it does not significantly affect that of pepsin. Such a finding is consistent with the specific action of the drug on parietal cells without an effect on the function of the pepsin-secreting chief cells.

Thompson et al. (1985) found no significant alteration in pepsin output after 4 weeks of omeprazole 20 or 40mg daily in 9 patients with duodenal ulcer disease. Omeprazole 10mg daily for 7 days did not affect basal or pentagastrin-stimulated pepsin in 6 healthy volunteers (Howden et al. 1985a), and a higher dosage of 30 or 60mg daily for 7 days did not affect basal pepsin secretion in healthy volunteers (Howden et al. 1984a). Similarly, 12 healthy subjects given omeprazole 40mg daily for 9 days did not display any alteration in pentagastrin-stimulated pepsin output (Festen et al. 1986).

2.7 Effect on Intragastric Bacteria and Bacterial Products

Ten healthy male subjects were given omeprazole 30mg daily for 2 weeks in the study of Sharma et al. (1984). Gastric juice sampled 22 hours after the final dose of omeprazole showed a significant ($p < 0.01$) rise in the concentrations of bacteria, nitrite and *N*-nitrosamines and a nonsignificant reduction in nitrate levels. The profound inhibition of gastric acidity had allowed proliferation of intragastric bacteria with consequent reduction of dietary nitrate to nitrite and the production of *N*-nitrosamines. All these changes had resolved within 3 days of stopping omeprazole.

2.8 Effects on Endocrine Function

The effects of high dose endocrine function have been studied in healthy male subjects (Howden et al. 1986b; MacGilchrist et al. 1987). Omeprazole 60mg daily for 8 days had no effect on the basal levels of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin (PRL), thyroxine (T_4), triiodothyronine (T_3), cortisol or testosterone. In addition, the responses of TSH and PRL to stimulation with thyrotrophin-releasing hormone and the responses of FSH and LH to stimulation with luteinising hormone–releasing hormone were unaffected by omeprazole.

An initial finding of a reduction in the peak cortisol level in response to stimulation with synthetic corticotrophin (ACTH) in a group of healthy male subjects receiving omeprazole 60mg daily for 8 days (Howden et al. 1986c) was not subsequently confirmed (MacGilchrist et al. 1987). However, *in vitro* studies using isolated bovine adrenocortical cells showed that incubation with omeprazole produces a marked dose-dependent inhibition of stimulated cortisol release (Howden et al. 1986c). This is unlikely to have any significance for the use of omeprazole in humans, since extremely high concentrations of omeprazole were necessary to produce the effect.

2.9 Effects on Renal Tubular Function

Omeprazole 60mg administered daily for 7 days did not affect 24-hour urinary electrolyte excretion or urinary acidification in response to oral ammonium chloride in a group of 8 healthy male subjects (Howden & Reid 1984).

3. Pharmacokinetics in Humans

3.1 Absorption and Serum Concentrations

Since omeprazole is acid-labile, it must be protected from the action of acidic gastric juice when given by mouth. In some studies, this was achieved by administering the drug with oral sodium bicarbonate (e.g. Cederberg et al. 1989). Absorption of omeprazole was rapid, with peak plasma concentrations being reached within 0.5h.

This drug is usually administered as encapsulated enteric-coated granules. The release from this formulation and subsequent absorption are erratic and do not follow classic pharmacokinetic princi-

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