

Pharmacodynamic Aspects of H₂-Blockers versus proton Pump Inhibitors

Cimetidine, ranitidine, famotidine and nizatidine, the currently marketed over-the-counter H₂ blockers, principally act via competitive inhibition of H₂ receptors located on the parietal cells of the stomach.

Omeprazole, the prototype proton pump inhibitor, is a highly specific inhibitor of the proton pump in the parietal cells of the stomach, thus inhibiting gastric acid secretion.

Both H₂ blockers and PPIs have been shown to cause dose-related suppression of basal gastric acid secretion. They both are potent antisecretory agents. However, they exhibit marked differences in their pharmacodynamic activities of inhibition of gastric secretion.

PPIs are themselves devoid of antisecretory activity. Under the highly acidic conditions found in the parietal cells, a PPI is converted to the active inhibitor, a protonated sulfanilamide, which binds covalently to the proton pump and inhibits it.

In general, while H₂-blockers have a rapid onset of action (< 1 hr) and a duration of less than 12 hrs, PPIs have a delayed onset of action and a prolonged duration of activity (up to 3 days).

The pharmacodynamics of famotidine is representative of the general pharmacodynamic characteristics of H₂ blockers. The onset of the antisecretory effect of famotidine is within 1 hr after oral administration, while the peak effect is achieved within 1-3 hrs. Inhibition of basal secretion by a single 40 mg oral dose of famotidine results in elevations of the intragastric pH to > 4.5 for up to 10-12 hrs (Chremos A, 1987).

PPIs have short half-lives ranging from 0.8-2 hrs. However, their effect can last for up to 3-5 days after drug administration. This is primarily attributed to their mechanism of action, which involves irreversible inhibition of the proton pump, hence, the rate limiting step in the antisecretory action of PPIs is the turnover rate of the pump, which has a half-life of 50 hrs. In contrast, the antisecretory activity of H₂-blockers is closely related to drug concentrations in plasma.

The results of two studies in patients with a history of heartburn who received single oral doses of omeprazole showed that at doses of up to 20 mg, omeprazole was not effective in increasing intragastric pH at 1 hr postdose. In one of the two studies, famotidine 10 mg raised intragastric pH greater than 4 more quickly than either the 10 or 20 mg doses of omeprazole (Lind et al, 1981, Fig. 1&2). In the other study, a single omeprazole 20 mg dose did not increase intragastric pH over the first 5 hrs postdose relative to placebo (AstraMerck, 1996, Fig. 3&4).

After repeated oral dosing, treatment with omeprazole, 20 mg once daily for 4 weeks, resulted in a median reduction of 97% in the 24-hr intragastric acidity (Lanzon et al, 1987).

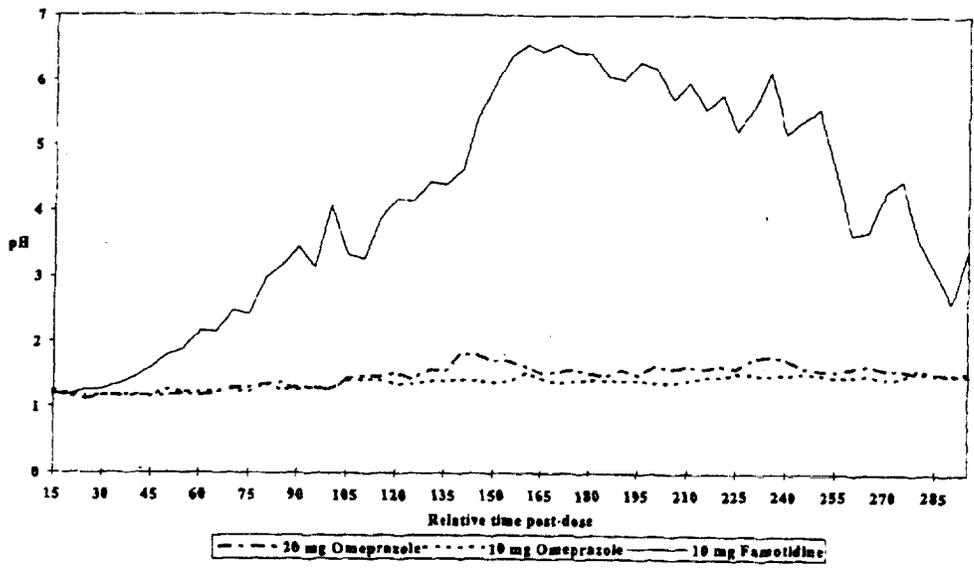
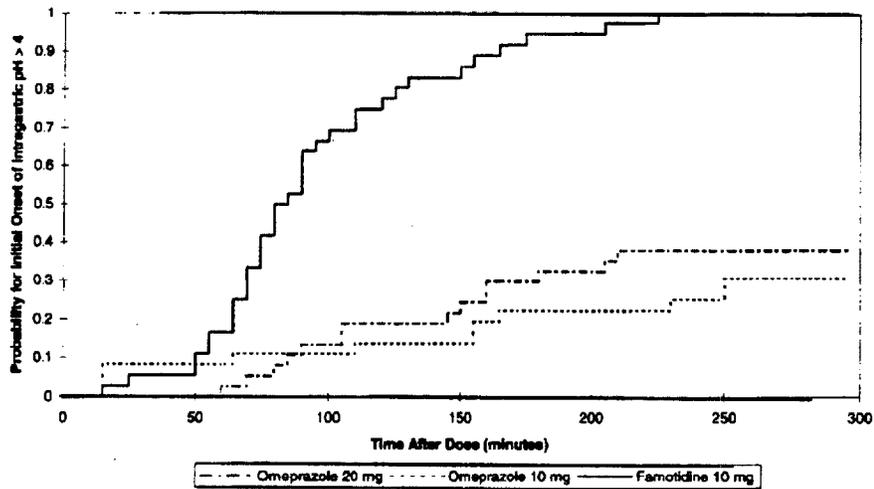


Fig. 1. Median 5 min intragastric pH values postdose by treatment



* Graph presents (1 - Kaplan-Meier estimates).

Fig. 2. Kaplan-Meier estimates for the time to onset of intragastric pH > 4 by treatment

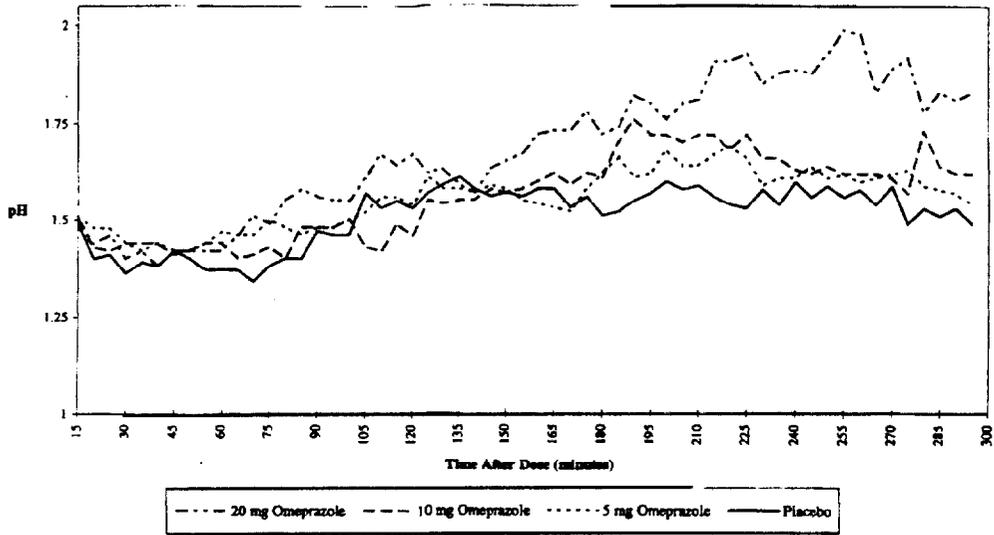
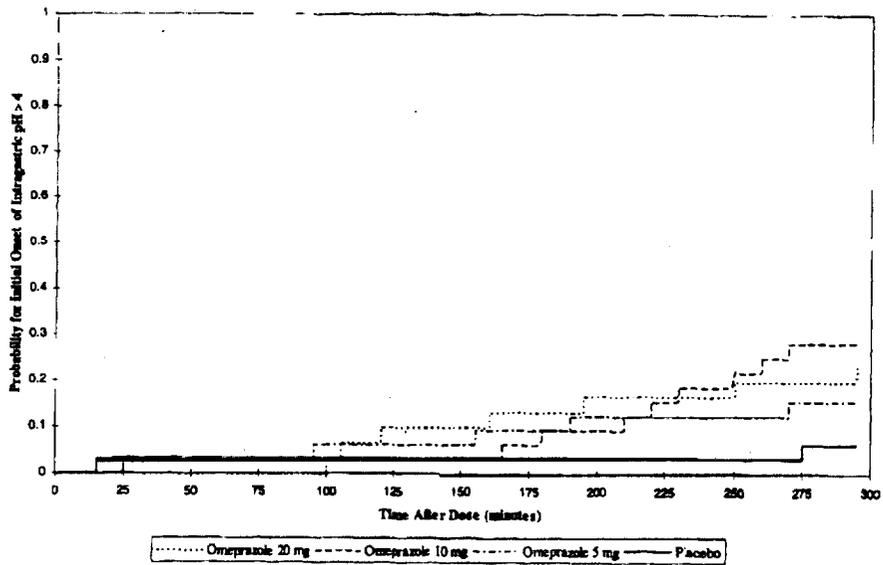


Fig. 3. Median 5 min intragastric pH values postdose by treatment



Graph presents (1 - Kaplan-Meier estimates).

Fig. 4. Kaplan-Meier estimates for the time to onset of intragastric pH > 4 by treatment