Effects of a Proton Pump Inhibitor, Omeprazole, on Gastric Secretion and Gastric and Duodenal Ulcers or Erosions in Rats

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The effects of omeprazole, a proton pump inhibitor, on gastric secretion and gastric or duodenal ulcers or erosions in rats were studied. Omeprazole, given intraduodenally, dose-dependently inhibited the gastric secretion (volume, acid and pepsin output) of pylorus-ligated rats. The antisecretory activity of omeprazole at 100 mg/kg persisted for 14 hr after treatment. Acutely induced gastric ulcers or erosions such as Shay ulcers, water-immersion stress-, indomethacin-, aspirin-, or prednisolone-induced erosions were all markedly inhibited by oral or intraduodenal administration of 10–100 mg/kg of omeprazole. The development of duodenal ulcers and gastric erosions caused by mepirizole was also potently inhibited by omeprazole at 3–10 mg/kg given orally. Repeated administration of omeprazole, 200 mg/kg/day in two divided doses for 14 days, significantly accelerated the spontaneous healing of acetic acid-induced gastric ulcers. The mechanism by which omeprazole inhibits the development of acute ulcers and accelerates healing of preexisting ulcers appears to be mainly due to its potent and long-lasting antisecretory activity. The antisecretory and antiulcer activities of omeprazole are equal to or exceed those of cimetidine, both in the maximum inhibitory response and ED$_{50}$ values.

Benzimidazole derivatives such as timoprazole, picoprazole, and omeprazole (Figure 1) inhibit gastric secretion in humans and experimental animals through a specific inhibition of the proton pump in parietal cells (1–5). Because of the potent and persisting antisecretory activities, these compounds have great potential in the treatment of peptic ulcer diseases. The present study was performed to examine whether or not one of those compounds, omeprazole, would inhibit gastric secretion and development of acute gastric and duodenal ulcers or erosions in rats. The effects of omeprazole on spontaneous healing of preexisting gastric ulcers were also given attention. Cimetidine was used as the reference drug.

MATERIALS AND METHODS

Male Sprague-Dawley rats (200–250 g, Charles-River, Japan) were used in all experiments.

Gastric Secretory Studies. Rats were deprived of food but allowed free access to water for 24 hr. Under ether anesthesia the abdomen was incised and the pylorus ligated. Seven or 14 hr after the pylorus ligation, the animals were given an overdose of ether and the gastric contents collected and analyzed for volume, acidity, and pepsin activity. Acidity was determined by automatic

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GASTROINTESTINAL PHARMACOLOGY OF OMEPRAZOLE

Fig 1. Chemical structure of omeprazole.

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\text{C}_3\text{H}_2\text{CH}_3\text{OCH}_3
\]

\[
\text{OCH}_2\text{S}\text{N}\text{H}_2\text{CH}_2\text{CH}_3\text{OCH}_3
\]

Titration of the gastric juice against 0.1 N NaOH to pH 7.0 (Autoburette, Radiometer). Pepsin activity was determined by Anson's method using bovine albumin as a substrate (6). Titratable acid and pepsin output were expressed as μg/hr and mg/hr, respectively. Omeprazole (Hässle) and cimetidine (Sigma) or the corresponding vehicle alone as a control was given intraduodenally (transmural injection) immediately after ligating the pylorus. The volume of each test drug, vehicle, or ulcerogenic agent was 0.5 ml/100 g body weight, unless otherwise noted. Omeprazole was suspended in 1% carboxymethylcellulose solution (CMC, w/v) containing 0.2% NaHCO₃ (w/v) and the pH was adjusted to 9.0 with 2 N NaOH. Cimetidine was suspended in 5% CMC.

Water-Immersion Stress-Induced Erosions. Rats not fasted prior to experiments were placed in a restraint cage, the same as the one described in detail elsewhere (7). The animals were then immersed vertically to the level of the xiphoid process in a water bath (23°C) for 7 hr (8) and killed. The stomach of each rat was removed and inflated by injecting 12 ml of 2% formalin to fix the inner and outer layers of the gastric walls. This formalin treatment was performed in all the following experiments. Subsequently, the stomach was incised along the greater curvature and examined for erosions in the glandular portion. Each drug or vehicle alone was given orally (gastric intubation) 10 min before stressing.

Shay Ulcers. Rats were deprived of food but allowed free access to water for 48 hr prior to experiments. Under ether anesthesia the abdomen was incised and the pylorus ligated (9). Fourteen hours later, the animals were killed, and the stomach was examined for ulcers in the forestomach. Each drug or vehicle alone was given intraduodenally immediately after pylorus ligation.

Indomethacin-Induced Erosions. Rats were deprived of food but allowed free access to water for 24 hr prior to experiments. Under ether anesthesia the abdomen was incised and the pylorus ligated (9). Fourteen hours later, the animals were killed, and the stomach was examined for erosions in the glandular portion. Each drug or vehicle alone was given orally 10 min before the indomethacin treatment.

Aspirin-Induced Erosions. Rats were deprived of food but allowed free access to water for 24 hr. Under ether anesthesia the abdomen was incised and the pylorus ligated. Aspirin (Merck) at 150 mg/kg, suspended in 1% CMC, was given orally 5 min after pylorus ligation (11). Seven hours later, the animals were killed, and the stomach was examined for erosions in the glandular portion. Each drug or vehicle alone was given intraduodenally immediately after pylorus ligation.

Prednisolone-Induced Erosions. A slightly modified method of Robert and Nezamis (12) was used. Rats not fasted prior to and during experiments were given prednisolone (Sigma) at 50 mg/kg subcutaneously in a volume of 0.25 ml/100 g body weight once daily (9:00 AM) for 4 days. Twenty-four hours after the final administration of prednisolone, the animals were killed, and the stomach was examined for erosions in the glandular portion. Each drug or vehicle alone was given orally twice daily (30 min before and 9 hr after prednisolone treatment) for 4 days.

Mepirizole-Induced Duodenal Ulcers and Gastric Erosions. Rats not fasted prior to experiments were given mepirizole (Daiichi) at 200 mg/kg, suspended in 1% CMC, orally and then deprived of both food and water (13). Twenty-four hours later, the animals were killed and the duodenum and stomach examined for ulcers in the duodenum and erosions in the antrum. Each drug or vehicle alone was given orally twice (30 min before and 9 hr after mepirizole treatment).

Acetic Acid-Induced Gastric Ulcers. In ether-anesthetized rats not fasted prior to experiments, the abdomen was incised and the anterior portion of the stomach exposed. Then 0.025 ml of 20% acetic acid (v/v) was injected into the submucosal layer at the junction of the fundus and antrum, i.e., about 1 cm proximal to the pylorus (14). Postoperatively, the animals were maintained on rat chow and water ad libitum. Each drug or vehicle alone was given orally from one day after the operation for 14 consecutive days twice daily (9:00 AM, 6:00 PM) to rats with gastric ulcers. The animals were killed 16 hr after the final administration of drugs and the stomach examined for ulcers.

Erosion or Ulcer Index. The length (mm) of each of the gastric erosions induced by water-immersion stress, indomethacin, aspirin, prednisolone, or mepirizole was measured under a dissecting microscope with a square grid (10×), summed, and used as an erosion index. Each area (mm²) of damaged mucosa in Shay ulcers was measured under a dissecting microscope (10×), summed, and arbitrarily classified into five degrees by an ulcer index as follows:

<table>
<thead>
<tr>
<th>Ulcerated area</th>
<th>1-6, 7-12, 13-18, 19-24, &gt;24 or (mm²)</th>
<th>Perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer index</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>

The area (mm²) of mepirizole-induced duodenal ulcers and acetic acid-induced ulcers was also measured and