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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.

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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

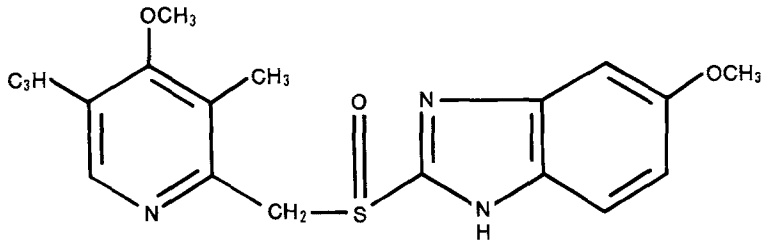

Fig 1. Chemical structure of omeprazole.

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 μeq/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% $NaHCO_3$ (w/v) and the pH was adjusted to 9.0 with 2 N NaOH. Cimetidine was suspended in 1% 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, and then indomethacin (Sigma) at 25 mg/kg, suspended in 1% CMC, was given subcutaneously (10). The animals were killed 7 hr later, 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, ie, 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 (mm^2) 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:

Ulcerated area (mm^2)	1–6	7–12	13–18	19–24	>24 or perforation
Ulcer index	1	2	3	4	5

The area (mm^2) of mepirizole-induced duodenal ulcers and acetic acid-induced ulcers was also measured and

used as an ulcer index. Ulcerated area of acetic acid ulcers was measured under a dissecting microscope with a higher magnification (16×). The person measuring the lesions had no knowledge of which treatment an animal had received.

Analysis of Data. Student's *t*-test was used to determine the statistical significance of the data and $P < 0.05$ was regarded as significant. The inhibitory ED_{50} (mg/kg) of omeprazole and cimetidine on gastric secretion and gastric or duodenal ulcers or erosions was calculated by the Litchfield-Wilcoxon method (15).

RESULTS

Effects on Gastric Secretion. Ligation of the pylorus for 7 hr produced an accumulation of gastric juice (about 10 ml/rat). When the ligation period was prolonged to 14 hr, the amount of accumulated gastric juice was more than 13 ml, on the average. At that time, several erosions or ulcers were observed in the forestomach, the incidence being 50–60%. Omeprazole, given intraduodenally, dose-dependently inhibited the gastric secretion (volume, acid and pepsin outputs) for 7 hr (Figure 2). The inhibition of acid output was all but complete when the compound was given in the dose of 100 mg/kg. Cimetidine also dose-dependently inhibited the volume, acid and pepsin outputs. However, the degree of inhibition by cimetidine at 200 mg/kg was weaker compared to that of 100 mg/kg of omeprazole. The antisecretory activity of omeprazole was observed even 14 hr after the intraduodenal administration. The inhibitions of volume, acid and pepsin outputs by 100 mg/kg of omeprazole were 51.5%, 86.1%, and 33.4%, respectively. Erosions or ulcers were not observed in the forestomach of rats treated with omeprazole. Cimetidine also significantly inhibited the acid output in the 14-hr experiment, but the degree of inhibition was less than 30%. One or two small erosions were found in the forestomach of 40–50% of animals treated with cimetidine.

Effects on Water-Immersion Stress-Induced Erosions. Water-immersion stress for 7 hr produced several linear and dotted erosions in the glandular stomach, the incidence being 100%. Omeprazole, given orally, dose-dependently inhibited water-immersion stress-induced erosions; the inhibition was 100% at 100 mg/kg (Figure 3). Cimetidine also significantly inhibited the erosions; the inhibition was 69.8% at 200 mg/kg.

Effects on Shay Ulcers. Ligation of the pylorus of rats for 14 hr produced multiple ulcers, including perforated ulcers, in the forestomach at the incidence of 100%. Omeprazole, given intraduodenally, dose-dependently inhibited the development of Shay ulcers; the inhibition was complete at 100 mg/kg (Figure 4). Cimetidine at 60 and 200 mg/kg had no significant effect on the ulcers.

Effects on Indomethacin-Induced Erosions. Indomethacin produced multiple erosions in the glandular stomach 7 hr after treatment. Omeprazole, given orally, dose-dependently inhibited the development of indomethacin-induced erosions (Figure 5). At 30 mg/kg, the inhibition was almost complete. Cimetidine also dose-dependently inhibited indomethacin-induced erosions; the inhibition was all but complete at 200 mg/kg.

Effects on Aspirin-Induced Erosions. Aspirin produced multiple, elongated erosions in the glandular stomach of pylorus-ligated rats, the incidence being 100%. Omeprazole, given intraduodenally, dose-dependently inhibited the erosions (Figure 6). Even at 1 mg/kg, the compound significantly inhibited the erosions (55.9%). The inhibition was all but complete at 30 mg/kg. Cimetidine also markedly inhibited the erosions, the inhibition being 97.3% at 60 mg/kg.

Effects on Prednisolone-Induced Erosions. Repeated administration of prednisolone for 4 days produced multiple and extensive erosions in the glandular stomach at the incidence of 100%. Omeprazole, given orally twice daily, dose-dependently inhibited the development of prednisolone-induced erosions (Figure 7). The inhibition was 87.2% at 200 mg/kg/day. Cimetidine also significantly inhibited the erosions; the inhibition was 69.3% and 67.9% with doses of 120 and 400 mg/kg/day, respectively.

Effects on Mepirizole-Induced Ulcers and Erosions. Mepirizole produced one or two penetrating ulcers in the proximal duodenum and two or three superficial erosions in the proximal antrum. Omeprazole, given orally twice, dose-dependently inhibited the development of both duodenal and gastric erosions (Figure 8). The inhibition of duodenal ulcers was 100% and that of gastric erosions was 72.7% at 20 mg/kg/day. Cimetidine also markedly inhibited the duodenal ulcers but tended to aggravate the gastric erosions.

Effects on Acetic Acid-Induced Gastric Ulcers. The submucosal injection of acetic acid solution produced visible and consistent ulcers (6×8 mm^2) in the stomach. Oral administration of omeprazole at 60 mg/kg/day tended to accelerate the healing of the ulcers (16.2%) (Figure 9). However, the agent at 200 mg/kg/day significantly accelerated the healing

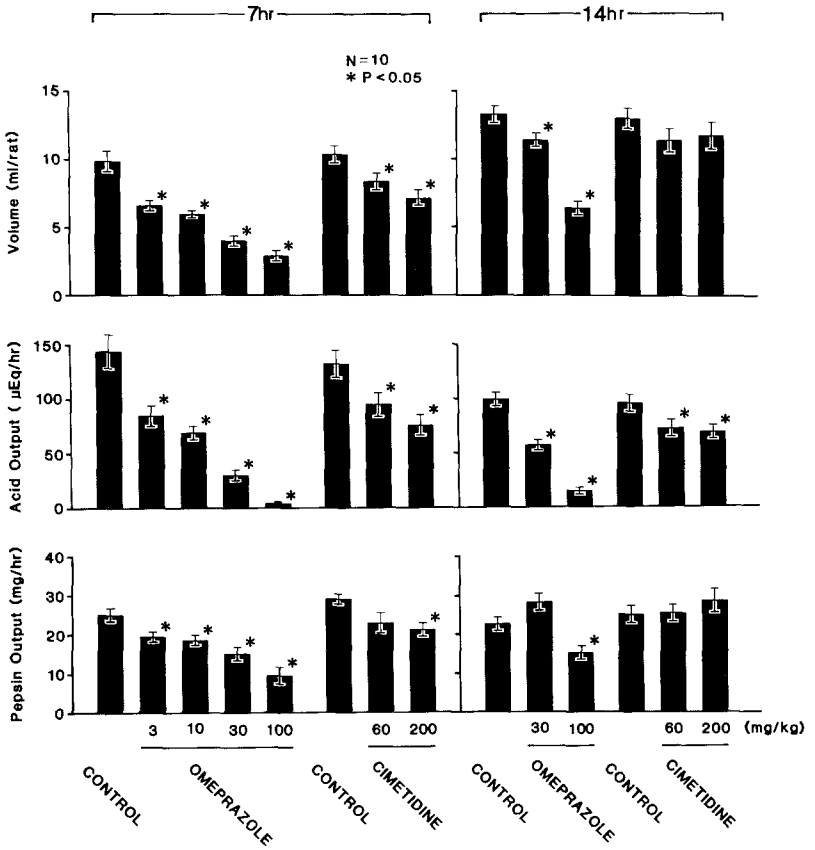

Fig 2. Effects of omeprazole and cimetidine on gastric secretion in pylorus ligated (7 or 14 hr) rats. * Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

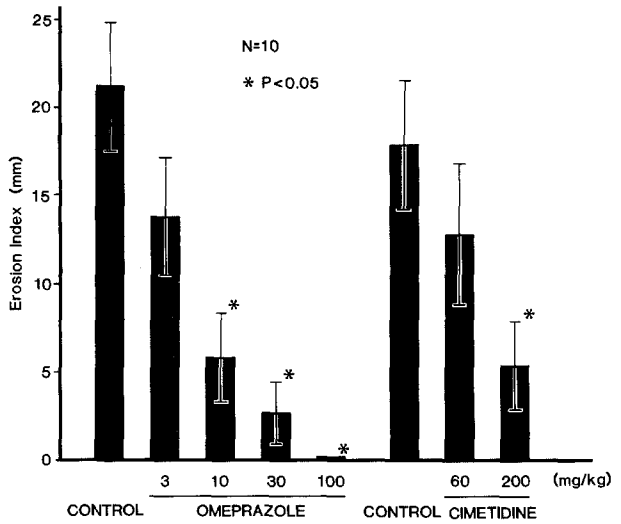

Fig 3. Effects of omeprazole and cimetidine on water-immersion stress-induced gastric erosions in rats. * Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

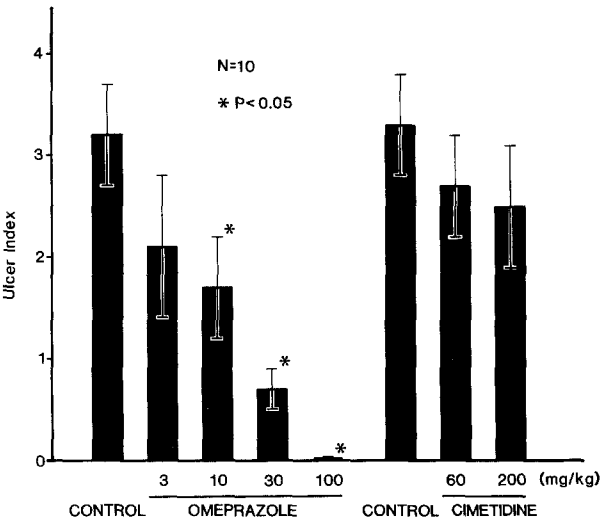

Fig 4. *Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

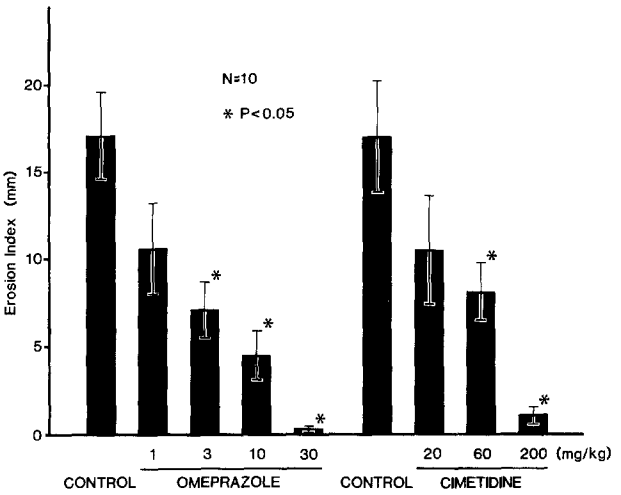

Fig 5. Effects of omeprazole and cimetidine on indomethacin-induced gastric erosions in rats. * Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

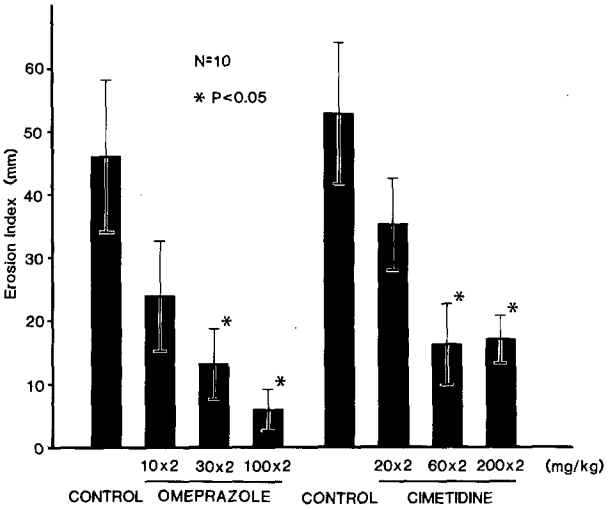

Fig 7. Effects of omeprazole and cimetidine on prednisolone-induced gastric erosions in rats. * Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

(37.8%). Cimetidine at 400 mg/kg/day tended to accelerate the healing of ulcers (15.8%).

ED_{50} Values. The ED_{50} values of omeprazole and cimetidine are given in Table 1. On basis of the ED_{50}, omeprazole is more potent than cimetidine by about 2.8–57.7 times. It should be noted that while the ED_{50} value of omeprazole on acid output after 7 hr ligation was 5.2 mg/kg, the value on aspirin- or indomethacin-induced erosions was 0.8 or 1.8 mg/kg, respectively. The same phenomenon was observed even with cimetidine; ie, the ED_{50} value on acid output was 300 mg/kg, whereas the value on water-immersion stress-, indomethacin-, or aspirin-induced erosions was 115.0, 39.9 or 7.2 mg/kg, respectively.

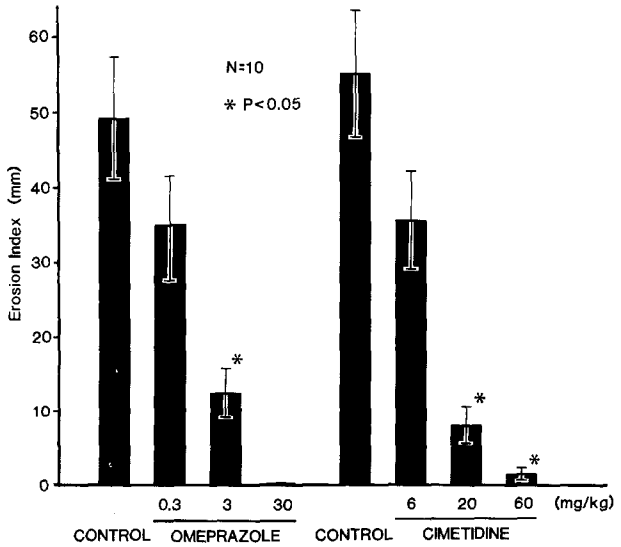

Fig 6. Effects of omeprazole and cimetidine on aspirin-induced gastric erosions in pylorus-ligated rats. * Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

DISCUSSION

The antisecretory effects of omeprazole have been observed in healthy subjects and in dogs (16, 17). Our present studies confirmed that omeprazole has a potent and long-lasting activity on gastric secretion in rats. The efficacy, duration, and ED_{50} values far exceeded or were lower than findings in the case of cimetidine. The doses used, as well as the ED_{50} values, were extraordinarily high compared to corresponding values obtained in dogs and humans. Whether this difference is due to rapid metabolism of the drugs in rats or to a low sensitivity of the rat secretory cells remains to be determined.

As expected from its antisecretory effect, omeprazole had a potent effect on various types of acutely-induced gastric ulcers or erosions in the dose range of 3–100 mg/kg. These findings suggest that gastric acid is crucially involved in the pathogenesis of water-immersion stress-, indomethacin-, aspirin-, or prednisolone-induced erosions or Shay ulcers. The ED_{50} of omeprazole and cimetidine on aspirin- or indomethacin-induced gastric erosions was considerably lower than that on acid output. Therefore, these agents seem to inhibit erosion

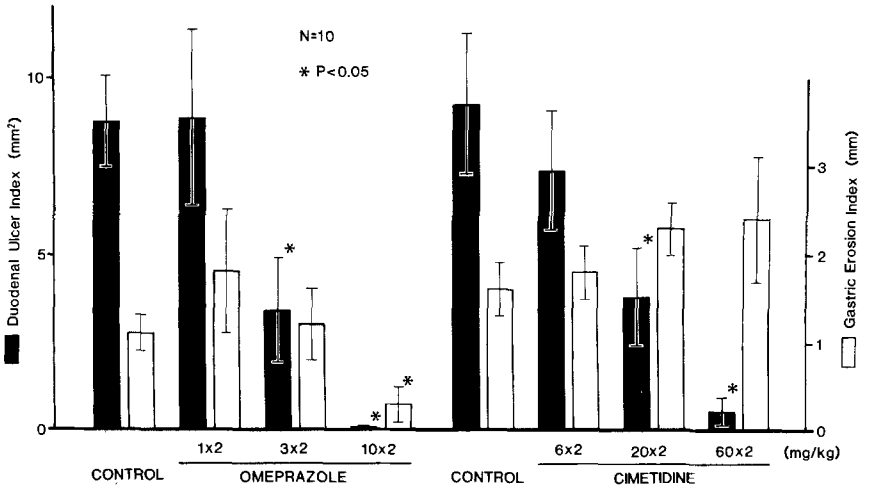

Fig 8. Effects of omeprazole and cimetidine on mepirizole-induced duodenal ulcers and gastric erosions in rats. * Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

formation partly by acid inhibition and partly by unknown mechanisms. Mattsson et al (18) reported that omeprazole given orally at 4.1–13.8 mg/kg significantly protected the rat gastric mucosa against various necrotizing agents. They stated that the protective effect of omeprazole is unrelated to the reduced acid secretion since the agent given intravenously significantly reduced the acid secretion but had no protective effect. They suggeted that omeprazole given orally has a cytoprotective activity on the gastric mucosa. Whether or not this cytoprotective activity is involved in the inhibition of various acute gastric lesions is the subject of ongoing experiments.

The precise mechanism of water-immersion stress-induced gastric erosions is unknown, but an increased gastric secretion was postulated by Kitagawa et al (19). In addition, an increased gastric motility during water-immersion stress may also play a role in the pathogenesis (20, 21). Larsson and Carlsson found that while omeprazole given orally at 138 mg/kg caused a delay in the rate of gastric

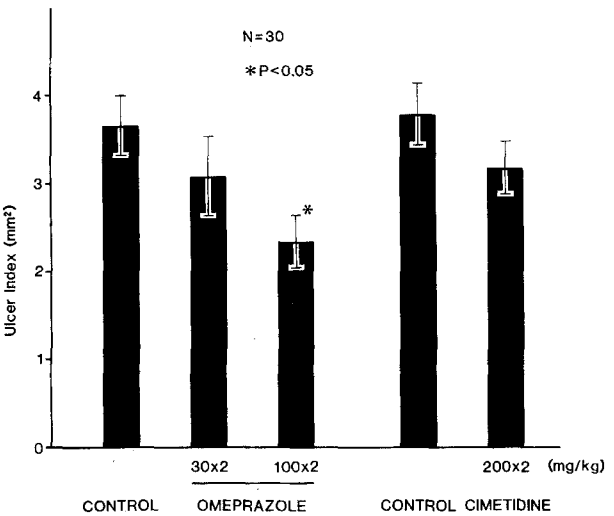

Fig 9. Effects of omeprazole and cimetidine on healing of acetic acid-induced gastric ulcers in rats. * Statistically different from controls ($P < 0.05$). All values represent mean ± SEM.

TABLE 1. ED_{50} VALUES OF OMEPRAZOLE AND CIMETIDINE

	ED_{50} (mg/kg)		*Ratio, cimetidine/ omeprazole*
	Omepra-zole	*Cimeti-dine*	
Gastric secretion			
7-hr ligation			
Volume	17.0		
Acid output	5.2	300	57.7
Pepsin output	51.5		
14-hr ligation			
Volume	96.0		
Acid output	35.0		
Pepsin output			
Gastric ulcers and erosions			
Water-immersion stress erosions	8.7	115.0	13.2
Shay ulcers	8.7		
Indomethacin erosions	1.8	39.9	22.2
Aspirin erosions	0.8	7.2	9.0
Prednisolone erosions	25.4	70.0	2.8
Duodenal ulcers and gastric erosions			
Mepirizole ulcers	5.4	29.0	5.4
Mepirizole gastric erosions	16.8		

emptying in rats, it had no effect on gastric emptying with doses of 13.8, 27.6, and 69 mg/kg (personal communication). Thus, the inhibition of water-immersion stress-induced gastric erosions by omeprazole, at least with doses of 10–30 mg/kg, is unlikely to be caused by an inhibition of gastric motility during stressing.

Cimetidine, used as a reference drug, also significantly inhibited the gastric secretion (volume, acid and pepsin output) for 7 hr. However, only the gastric acid output was inhibited up to 14 hr after the treatment with cimetidine in doses of 60 and 200 mg/kg. Cimetidine also potently inhibited water-immersion stress-, indomethacin-, aspirin-, and prednisolone-induced gastric erosions but not Shay ulcers. Cimetidine had no effect on Shay ulcers which developed under the condition of 14 hr ligation of the pylorus, probably because of the short duration of antisecretory activity.

In the foregoing work we found that, while cimetidine potently inhibited mepirizole-induced duodenal ulcers, it aggravated the development of gastric erosions (13). In the present study, cimetidine showed no significant aggravation of mepirizole-induced erosions, but this agent did tend to enhance erosion formation. In contrast to cimetidine, omeprazole significantly inhibited both the duodenal and gastric erosions in response to mepirizole. These results provide evidence that both lesions were induced by the corrosive activity of gastric juice. It is likely that the antisecretory effect of cimetidine is too weak to sufficiently suppress the gastric erosions caused by mepirizole.

It should be noted that omeprazole significantly accelerated the spontaneous healing of preexisting gastric ulcers. Agents such as aluminum sucrose sulfate, 15-methyl-PGE_2, and IBI-C83 reportedly accelerate the healing process of acetic acid-induced gastric ulcers in rats (22–24). The efficacy of aluminum sucrose sulfate is postulated to be due to its binding activity with the ulcerated area so as to protect it from further invasion of corrosive gastric jucie (25, 26). The effects of the latter two agents are probably due to their cytoprotective and antisecretory actions. Delayed gastric emptying is generally an unfavorable factor with regard to healing of peptic ulcers in man. One of the present authors (S.O.) reported that prolonged treatment with propantheline bromide and surgical vagotomy significantly delayed the healing of acetic acid ulcers in rats (8, 22). While omeprazole at 138 mg/kg does inhibit gastric emptying, it accelerates the healing of preexisting ulcers. This suggests that the antisecretory activity of omeprazole makes up for the unfavorable activity on gastric emptying.

All these findings taken together indicate that omeprazole is a most promising agent for the treatment of both gastric and duodenal ulcers.

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