Antisecretory and Antiulcer Effects of YM020, a New \( \text{H}^+\text{,K}^+\)-ATPase Inhibitor, in Rats and Dogs

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ABSTRACT We examined the effects of YM020 (3-cyanomethyl-2-methyl-8-[(3-methyl-2-butenyl)oxy]-imidazo[1,2-a]pyridine), a novel \( \text{H}^+\text{,K}^+\)-ATPase inhibitor, on gastric acid secretion and experimental gastroduodenal lesions in rats and dogs. Intraduodenal, subcutaneous and oral YM020 inhibited basal gastric acid secretion in pylorus-ligated rats with ED\(_{50}\) values of 9.1, 9.1 and 9.5 mg/kg, respectively. Oral pretreatment with YM020 5 hr before ligation still suppressed acid secretion, with a potency a little less than that of omeprazole. In anesthetized dogs, intravenous YM020 inhibited histamine-, methacholine- and pentagastrin-induced gastric acid secretion with ED\(_{50}\) values of 0.05, 0.01 and 0.08 mg/kg, respectively. In Heidenhain pouch dogs, although oral YM020 (3 mg/kg) inhibited histamine-induced acid secretion, acid output returned to control levels faster than in dogs treated with omeprazole. Oral YM020 inhibited the formation of water-immersion restraint stress-, indomethacin-, absolute ethanol-, 0.7 N hydrochloric acid- and cysteamine-induced gastric or duodenal lesions with ED\(_{50}\) values of 2.9, 4.3, 2.0, 11.7 and 8.4 mg/kg, respectively. Moreover, subcutaneous YM020 also suppressed the formation of ethanol- and HCl-induced gastric lesions. These results suggest that YM020 has an antisecretory effect almost the same as or 2 to 3 times weaker than those of omeprazole and that its duration is not as long as that of omeprazole in rats and dogs. Furthermore, YM020 possesses a cytoprotective effect and the mechanism of YM020 may be different to that of omeprazole.

Keywords: YM020, Proton pump inhibitor, Omeprazole, Famotidine, Cimetidine, Cytoprotection

Peptic ulcer results from a disturbance in the balance between forces tending to injure the gastric mucosa and the ability of the mucosa to withstand these forces or to rapidly repair ulcerating lesions as they occur. Several kinds of drugs that alkalify intra-gastrical acidity (e.g. antacid, muscarinic antagonists, histamine \( \text{H}_2\)-antagonists, etc.) are used to treat peptic ulcer, indicating the important role of gastric acid in injury to the gastric mucosa.

In 1973, Ganser and Forte (1) established that the \( \text{H}^+\text{,K}^+\)-ATPase found in the parietal cells is involved in the terminal step of gastric acid secretion. This finding triggered many investigations to find an inhibitor of \( \text{H}^+\text{,K}^+\)-ATPase. In 1983, Wallmark et al. (2, 3) first reported that omeprazole was an inhibitor of this enzyme. Omeprazole potently suppresses gastric acid secretion (4–6) with an effect that lasts for 3 days in dogs (4) and humans (7). This potent and long-lasting antisecretory effect is reported to be due to the drug’s irreversible binding to the sulf-hydryl (SH) group of the \( \text{H}^+\text{,K}^+\)-ATPase molecule (8). However, continuous long-term administration of omeprazole has been shown to induce the development of gastric carcinoid in experimental animals (9). This unwanted side effect is now thought to reflect the fact that pharmacological blockade of acid secretion results in long-lasting hypergastrinemia, which in turn gives rise to hyperplasia of certain endocrine cells, the so-called ECL (enterochromaffin-like) cells (10, 11).

SCH 28080 was described to be an antiulcer compound with both antisecretory and cytoprotective properties (12, 13). This compound, unlike omeprazole, is a reversible and competitive inhibitor of the \( \text{H}^+\text{,K}^+\)-ATPase in parietal cells with high affinity at the \( \text{K}^+\)-site (12–15), and it potently inhibits gastric acid secretion with a duration of action the same as or shorter than that of cimetidine (14, 15).

In 1990, Kamato et al. (16) reported that YM020 (Fig. 1), a novel and reversible \( \text{H}^+\text{,K}^+\)-ATPase inhibitor, competitively suppresses this enzyme at the \( \text{K}^+\)-binding site. In the present paper, we examined the antisecretory and antiulcer effects of YM020 and compared the results with...
those of omeprazole in rats and dogs.

MATERIALS AND METHODS

Antisecretory effects

**Basal gastric acid secretion in pylorus-ligated rats:** Male Wistar rats weighing 200–250 g were used. They were fasted 24 hr prior to the experiment with free access to water. Under light ether anesthesia, the abdomen was incised and the pylorus was ligated. They were placed in individual mesh cages to prevent coprophagy. Four hours later, the animals were killed with ether, and the gastric contents were collected and analyzed for volume and acidity. Acidity was determined by automatic titration of the gastric juice with 0.05 N NaOH to pH 7.0 (Comtite-7; Hiranuma, Tokyo). Drugs or vehicle were orally dosed 1 hr before ligation, intraduodenally administered immediately after ligation, or subcutaneously injected 30 min before ligation.

In other experiments to investigate the duration of the effects of drugs, oral doses were administered 1 and 5 hr before ligation.

**Gastric acid secretion in anesthetized dogs:** Adult mongrel dogs of both sexes weighing 6–18 kg were used. After being fasted for 24 hr with free access to water, they were anesthetized with sodium pentobarbital (30 mg/kg, i.v.), and a stainless steel cannula was introduced through the ventral wall of the stomach after ligation of the pylorus and esophagus. The gastric juice was collected from the gastric cannula by gravity drainage every 15 min. Drugs were intravenously given after gastric secretion induced by intravenous infusion of histamine (160 μg/kg/hr), methacholine (100 μg/kg/hr) or pentagastrin (8 μg/kg/hr) reached a steady state. Acidity of the gastric juice was measured as described above for rats.

**Gastric acid secretion in Heidenhain pouch dogs:** Eight male Beagle dogs weighing 7–12 kg were used. A Heidenhain pouch was prepared by the conventional method under anesthesia with a combination of nitrous oxide, oxygen and halothane. One month after preparation of the pouch, secretory experiments were performed once a week in each animal throughout the experiments. The animals were fasted with free access to water for 18 hr before each experiment. Gastric juice was collected from the gastric pouch cannula by gravity drainage every 15 min. Acidity of the gastric juice was measured as for rats. Histamine (40 μg/kg/hr) was infused intravenously via a cannula intubated in the hind limb. Drugs were given orally after gastric secretion induced by histamine reached a steady state.

**Antiulcer effects**

**Water-immersion restraint stress-induced gastric lesion:** Male Wistar rats weighing 200–250 g were used after fasting for 18 hr with free access to water. Investigations were conducted according to a previously reported method (17). Animals were individually immobilized in each compartment of a stress cage. The cages were then immersed vertically in a water bath kept at 23°C for 7 hr to the height of the xiphoid of the animals. The stomach was cut open along the greater curvature and spread over the pad. The length of each lesion was measured, and the sum of the lengths of all lesions in each stomach was used as the lesion index. Drugs or vehicle were administered orally 1 hr before or subcutaneously 30 min before the start of immersion.

**Indomethacin-induced gastric lesion:** Male Wistar rats weighing 200–230 g were used after fasting for 18 hr with free access to water. A previously reported method (18) was modified to induce deeper ulceration. Animals were killed 5 hr after subcutaneous injection of indomethacin (20 mg/kg), and the stomachs were examined for lesions. Drugs or vehicle were given orally 1 hr before the administration of indomethacin.

**Ethanol-induced gastric lesion:** Male Wistar rats weighing 210–250 g were used after being deprived of food for 24 hr and water for 18 hr. Animals were killed 1 hr after oral administration of 1 ml/animal of absolute ethanol (99.5% v/v), and the stomachs were examined for lesions. Drugs or vehicle were given orally 1 hr or subcutaneously 30 min before the administration of ethanol.

**HCl-induced gastric lesion:** Male Wistar rats weighing 200–250 g were used after being deprived of food for 24 hr and water for 18 hr. Animals were killed 1 hr after oral administration of 1 ml/animal of 0.7 N HCl solution, and the stomachs were examined for lesions. Drugs or vehicle were given orally 1 hr or subcutaneously 30 min before the administration of HCl.

**Cysteamine-induced duodenal lesion:** Male Wistar rats weighing 220–270 g were used after fasting for 18 hr with free access to water. A modification of the methods of Fujii and Ishii (19) was used. Animals were killed 18 hr af-
ter subcutaneous injection of cysteamine (300 mg/kg). The duodenum was cut open along the longitudinal axis and spread over the pad. The length of each lesion was measured, and the sum of the lengths of all lesions in each duodenum was used as the lesion index. Drugs or vehicle were given orally 1 hr before the administration of cysteamine.

Drugs
YM020 (YM19020; 3-cyanomethyl-2-methyl-8-[3-methyl-2-butenyl]oxy]imidazo[1,2-a]pyridine), omeprazole, famotidine and cimetidine were prepared at Yamanouchi Pharmaceutical Co., Ltd. Histamine dihydrochloride, pentagastrin (Sigma, St. Louis, MO, USA) and methacholine chloride (Nacalai Tesque, Kyoto) were obtained commercially. In experiments using subcutaneous and intravenous injection, famotidine and cimetidine were dissolved in a minimal quantity of N/10 hydrochloric acid and diluted with saline, while the others were dissolved and diluted with saline. Drugs given orally and intraduodenally to rats were suspended in 0.5% methylcellulose solution, and those given orally to dogs were filled in gelatin capsules. All drug doses were in terms of the free base.

Statistics
All values represent the means±S.E.M. or the mean with 95% confidence limits. Values for gastric secretion in pylorus-ligated rats and gastric lesion in conscious rats represent the percent inhibition determined with reference to concomitantly tested control animals. Values for gastric secretion in anesthetized and Heidenhain pouch dogs represent the percent inhibition determined by comparing acid output obtained after dosing a test drug in each time with that obtained just before dosing. ED₅₀ values and 95% confidence limits were determined by probit analysis from the data obtained for three to four doses of each compound. Statistical significance was determined by analysis of variance. Differences among groups were compared by the Newman-Keuls multiple range test. Probabilities of <5% (P < 0.05) were considered significant.

RESULTS
Antisecretory effects
Basal gastric secretion in pylorus-ligated rats: Basal gastric acid secretion in pylorus-ligated rats was 241.3 ± 19.2 μEq over 4 hr. YM020 (3–30 mg/kg) dose-dependently inhibited basal acid secretion in pylorus-ligated rats by all treatment routes (Fig. 2). ED₅₀ values (95% confidence limits) in oral, intraduodenal and subcutaneous treatment were 9.5 (5.0–18.0), 9.1 (7.9–10.5) and 9.1 (7.8–10.6) mg/kg, respectively. Intraduodenal and subcutaneous omeprazole inhibited basal gastric acid secretion (Fig. 2) with ED₅₀ values of 2.5 (2.2–2.9) and 4.7 (3.1–7.1) mg/kg, respectively.

Oral pretreatment with YM020 for 1 and 5 hr also inhibited basal acid secretion in pylorus-ligated rats with ED₅₀ values (95% confidence limit) of 9.5 (5.0–18.0) and 37.1 (31.0–44.5) mg/kg, respectively (Fig. 3). The ratio of ED₅₀ values of 1 to 5 hr pretreatment for YM020 was 3.9. This ratio is not as good as that for omeprazole (=2.4), but much better than those for famotidine (=62.9) and cimetidine (=56.7) (Table 1).

Gastric acid secretion in anesthetized dogs: Gastric acid secretion induced by histamine (160 μg/kg/hr), methacholine (100 μg/kg/hr) and pentagastrin (8 μg/kg/hr) in the steady state was 2725.4±193.6, 1207.3±286.8 and 864.5±266.3 μEq/15 min, respectively.

Intravenous injection of YM020 inhibited histamine (160 μg/kg/hr)-, methacholine (100 μg/kg/hr)- and pen-
Fig. 3. Effects of 1 (○) and 5 (△) hr pretreatment of YM020 and omeprazole on 4-hr basal gastric acid secretion in pylorus-ligated rats. Each value represents the mean±S.E.M. of 10 animals. *: P<0.05, **: P<0.01, ***: P<0.001, vs acid output of the vehicle-treated control group.

Table 1. Duration of action of YM020, omeprazole, famotidine and cimetidine in pylorus-ligated rats

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ED50 (mg/kg, p.o.) (95% confidence limits)</th>
<th>1-hr pretreatment (A)</th>
<th>5-hr pretreatment (B)</th>
<th>(B)/(A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YM020</td>
<td>9.5 (5.0–18.0)</td>
<td>37.1 (31.0–44.5)</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>7.7 (1.7–35.0)</td>
<td>18.6 (15.6–22.3)</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td>0.42 (0.14–1.28)</td>
<td>26.4 (11.3–61.3)</td>
<td>62.9</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>28.9 (13.0–64.1)</td>
<td>1640 (1098–2449)</td>
<td>56.7</td>
<td></td>
</tr>
</tbody>
</table>

*: Drugs were dosed orally 1 or 5 hr before pylorus ligation

Fig. 4. Effects YM020 (open columns) and omeprazole (hatched columns) on histamine (160 μg/kg/hr)-, methacholine (100 μg/kg/hr)- and pentagastrin (8 μg/kg/hr)-induced gastric acid secretion in anesthetized dogs. Drugs were given intravenously after gastric acid secretion induced by intravenous infusion of each secretagogue reached a steady state, and effects were calculated from maximal inhibition. Each value represents the mean ±S.E.M. of 3 to 5 animals. *: P<0.05, **: P<0.01, ***: P<0.001, vs acid output just before the drug administration.

Pentagastrin

Histamine

Methacholine

Table 1. Duration of action of YM020, omeprazole, famotidine and cimetidine in pylorus-ligated rats

- Gastric acid secretion in Heidenhain pouch dogs: Oral treatment with YM020 at doses of 3 to 8 mg/kg and omeprazole at 0.1 to 1 mg/kg inhibited histamine (40 μg/kg/hr)-induced gastric acid secretion in Heidenhain pouch dogs (Figs. 5 and 6). ED50 values (95% confidence limits) of YM020 and omeprazole calculated from the maximum inhibition were 1.2 (1.0–1.4) and 0.36 (0.29–0.43) mg/kg, respectively.

- The effects of the drug were as potent as those of omeprazole in histamine- and pentagastrin-induced gastric acid secretion and more potent than that of omeprazole in methacholine-induced secretion (Fig. 4).

Gastric acid secretion in Heidenhain pouch dogs: Oral treatment with YM020 at doses of 3 to 8 mg/kg and omeprazole at 0.1 to 1 mg/kg inhibited histamine (40 μg/kg/hr)-induced gastric acid secretion in Heidenhain pouch dogs (Figs. 5 and 6). ED50 values (95% confidence limits) of YM020 and omeprazole calculated from the maximum inhibition were 1.2 (1.0–1.4) and 0.36 (0.29–0.43) mg/kg, respectively.
Fig. 5. Effects of oral treatment of 1 (○), 3 (△), 5 (□) and 8 (▲) mg/kg of YM020 on histamine (40 μg/kg/hr)-induced gastric acid secretion in Heidenhain pouch dogs. Drugs were given orally after gastric acid secretion induced by intravenous infusion of histamine reached a steady state. Each value represents the mean±S.E.M. of 2 to 8 animals. *: P<0.05, vs acid output just before the drug administration.

Fig. 6. Effects of oral treatment of 0.1 (○), 0.3 (△) and 1 (□) mg/kg of omeprazole on histamine (40 μg/kg/hr)-induced gastric and secretion in Heidenhain pouch dogs. Drugs were given orally after gastric acid secretion induced by intravenous infusion of histamine reached a steady state. Each value represents the mean±S.E.M. of 2 to 8 animals. *: P<0.05, vs acid output just before the drug administration.

Fig. 7. Effects of oral treatment of 3 mg/kg of YM020 (○), 1 mg/kg of omeprazole (●), 0.03 mg/kg of famotidine (▲) and 1 mg/kg of cimetidine (■) on histamine (40 μg/kg/hr)-induced gastric acid secretion in Heidenhain pouch dogs. Each value represents the mean±S.E.M. of 4 to 8 animals. *: P<0.05, vs acid output just before the drug administration.

The inhibitory effects of YM020 at 3, 5 and 8 mg/kg disappeared at 2.5, 3 and 3.5 hr after treatment, respectively (Fig. 5), whereas that of omeprazole (1 mg/kg) continued for 4 hr (Fig. 6), showing that the duration of action of YM020 was shorter than that of omeprazole. The inhibitory effects of single doses (approximating the ED₅₀ value calculated from maximum inhibition after dosing) of test compounds were compared to evaluate their duration of action. Results showed that the duration of action of YM020 was almost equal to those of famotidine and cimetidine (Fig. 7).

Antiulcer effects

Water-immersion restraint stress-induced gastric lesion: Water-immersion restraint stress resulted in hemorrhagic damage along the long axis of the stomach with a lesion index of 9.3±1.3 mm. Oral treatment with YM020 and omeprazole dose-dependently suppressed water-immersion restraint stress-induced gastric lesion formation (Fig. 8) with ED₅₀ values (95% confidence limits) of 2.9 (2.3–3.6) and 10.4 (5.3–20.3) mg/kg, respectively. Subcutaneous injections of YM020 and omeprazole also inhibited lesion formation with ED₅₀ values (95% confidence limits) of 4.3 (3.8–4.8) and 7.6 (3.2–10.1) mg/kg, respectively (Fig. 8).

Indomethacin-induced gastric lesion: Administration of indomethacin at 20 mg/kg, s.c. produced gastric lesions with a lesion index of 7.3±1.7 mm. As shown in Fig. 9, oral treatment with YM020 and omeprazole at doses of 3 to 30 mg/kg dose-dependently inhibited indomethacin-induced gastric lesion formation (Fig. 9) with ED₅₀ values (95% confidence limits) of 4.3 (2.3–8.0) and 4.8 (2.3–9.9) mg/kg, respectively.

Ethanol-induced gastric lesion: When absolute ethanol was given to the control animals, multiple severe lesions were induced in the glandular portion of the stomach, with a lesion index of 46.3±3.6 mm. Oral treatment with YM020 at doses of 3 and 10 mg/kg and omeprazole at 30 mg/kg suppressed this ethanol-induced gastric lesion formation (Fig. 10) with ED₅₀ values (95% confidence limits) of 2.0 (1.7–2.3) and 6.9 (4.3–11.3) mg/kg, respectively.

On subcutaneous injection, YM020 at doses of 1 to 10
Fig. 9. Effects of oral YM020 (open columns) and omeprazole (hatched columns) on the formation of indomethacin (20 mg/kg, s.c.)-induced gastric lesions in rats. Drugs or vehicle were given 1 hr before the administration of indomethacin. Five hours after indomethacin, animals were killed, and the lesion index was measured. Each value represents the mean±S.E.M. of 9 to 10 animals. *: P<0.05, **: P<0.01, ***: P<0.001, vs gastric lesion index of the vehicle-treated control group.

mg/kg also significantly inhibited the lesion formation with an ED50 value (95% confidence limits) of 1.1 (0.5–2.4) mg/kg. In contrast, omeprazole at 10 and 30 mg/kg did not affect ethanol-induced gastric lesions (Fig. 10).

HCl-induced gastric lesion: Intragastric administration of 0.7 N HCl produced hemorrhagic damage along the long axis of the stomach, with a lesion index of 49.2±2.4 mm. Oral treatment with YM020 at doses of 10 and 30 mg/kg and omeprazole at doses of 30 and 100 mg/kg significantly suppressed HCl-induced gastric lesion formation (Fig. 11) with ED50 values (95% confidence limits) of 11.7 (9.7–14.1) and 28.7 (22.6–36.5) mg/kg, respectively.

On subcutaneous injection, YM020 at 1 to 10 mg/kg also inhibited lesion formation in a dose-dependent manner, with an ED50 value (95% confidence limits) of 2.6 (2.0–3.4) mg/kg. In contrast, omeprazole at 30 mg/kg did not affect the formation (Fig. 11).

Cysteamine-induced duodenal lesion: In the control animals, severe hemorrhagic lesions were induced in the duodenal mucosa with a lesion index of 18.1±2.2 mm. Oral treatment with YM020 at a dose of 30 mg/kg and omeprazole at doses of 3, 10 and 30 mg/kg significantly suppressed cysteamine-induced duodenal lesion formation (Fig. 12) with ED50 values (95% confidence limits) of 8.4 (6.4–10.9) and 6.0 (2.0–18.3) mg/kg, respectively.

DISCUSSION

Gastric acid approximately corresponds to 0.16 N hydrochloric acid. It is secreted from parietal cells located in the mucosa of the fundus and body of the stomach. The ionic pump, which produces the primary transport event, is a K+-stimulated ATP-hydrolyzing membrane-bound enzyme called H^+\cdotK^-\text{ATPase}. This pump utilizes ATP to catalyze the transmembrane exchange of H^+ from the cell to the lumen and that of K^- from the lumen to the cell. Omeprazole, which was first described in 1983 (2, 3), irreversibly binds to the SH group of H^+\cdotK^-\text{ATPase} (8), and it potently inhibits gastric acid secretion in rats and dogs for a prolonged period (4–7). It was reported that omeprazole produces hyperplasia of oxyntic mucosal cells, including the hyperplasia of endocrine enterochromaffin-like cells and the development of gastric carcinoid in rats (9). These actions are now thought to be due not to any direct action of omeprazole, but rather to...
Fig. 10. Effects of oral and subcutaneous YM020 (open columns) and omeprazole (hatched columns) on the formation of absolute ethanol-induced gastric lesions in rats. Drugs or vehicle were given orally 1 hr or subcutaneously 30 min before the administration of absolute ethanol. One hour after ethanol, the animals were killed, and the lesion index was measured. Each value represents the mean ± S.E.M. of 5 to 15 animals. **: P<0.01, ***: P<0.001, vs gastric lesion index of the vehicle-treated control group.

Fig. 11. Effects of oral subcutaneous YM020 (open columns) and omeprazole (hatched columns) on the formation of 0.7 N HCl-induced gastric lesions in rats. Drugs or vehicle were given orally 1 hr or subcutaneously 30 min before the administration of 0.7 N HCl. One hour after HCl, the animals were killed and the lesion index was measured. Each value represents the mean ± S.E.M. of 5 to 10 animals. **: P<0.01, ***: P<0.001, vs gastric lesion index of the vehicle-treated control group.

the trophic effect of endogenous gastrin. That is, omeprazole inhibits gastric acid secretion completely and for a prolonged period, and this achlorhydria induces the release of gastrin into the blood. This hypergastrinemia produces hyperplasia of ECL cells though the proliferous action of gastrin (10, 11, 20).

Long et al. (12) showed that SCH 28080 inhibited gastric acid secretion in rats, guinea pigs and dogs. The antisecretory and antiulcer potency of the compound is the same as or superior to that of cimetidine (13). Furthermore, the compound has been shown to possess a cytoprotective effect (13). SCH 28080 is a highly selective inhibitor of the parietal cell K⁺/H⁺-ATPase, but the mechanism of the antisecretory effects of this compound, unlike that of omeprazole, is competitive and reversible interaction with the high affinity K⁺-site of gastric ATPase, with the result that this compound inhibits K⁺ influx and gastric acid secretion competitively and reversibly (14, 15).

Recently, YM020, an imidazopyridine derivative (Fig. 1) structurally independent of omeprazole, was synthesized as a novel H⁺,K⁺-ATPase inhibitor. Kamato et al. (16) have reported that YM020 suppresses this enzyme competitively at the K⁺-binding site and that the compound acts directly, unlike the mechanism of omeprazole, which may need transformation to the active metabolite for inhibition of the enzyme (21). It is therefore possible that because this drug inhibits gastric acid secretion potently but for only a short-term duration, YM020 has no side effects such a hyperplasia of endocrine enterochromaffin cells and gastric carcinoid.

In the present study, the antisecretory effect of YM020 was examined using basal gastric secretion in pylorus-ligated rats and secretagogue-stimulated gastric secretion.
Fig. 12. Effects of oral YM020 (open columns) and omeprazole (hatched columns) on the formation of cysteamine (300 mg/kg, s.c.)-induced duodenal lesion in rats. Drugs or vehicle were given orally 1 hr before administration of cysteamine. Eighteen hours after cysteamine, the animals were killed, and the lesion index was measured. Each value represents the mean±S.E.M. of 5 to 10 animals. *: P<0.05, **: P<0.01, ***: P<0.001, vs gastric lesion index of the vehicle-treated control group.

in anesthetized dogs and conscious Heidenhain pouch dogs. Comparison of the results with those of omeprazole showed that the inhibitory effect of YM020 on gastric secretion in rats and dogs was almost the same as or 2 to 3 times weaker than that of omeprazole. Moreover, pharmacological bioavailability, as evaluated by the p.o.-to-i.v. (s.c.) ED$_{50}$ ratio of YM020, is better than that of omeprazole in rats, but is slightly inferior to that of omeprazole in dogs.

To evaluate the duration of the antisecretory effects of the test compounds, ED$_{50}$ values obtained with the oral pretreatment times of 1 and 5 hr pylorus-ligated rats were compared. The ED$_{50}$ ratio of 5 hr to 1 hr for YM020 was 3.9, which was not as good as that for omeprazole (2.4), but better than those for famotidine (62.9) and cimetidine (56.7). In Heidenhain pouch dogs, oral administration of YM020 at a dose of 3 mg/kg inhibited the gastric acid secretion induced by histamine. The inhibitory effect of YM020 was eliminated as fast as that of famotidine and cimetidine, but the antisecretory effect of omeprazole was maintained at least for 4.5 hr after treatment. Furthermore, a difference was seen in the duration of action of YM020 in rats and dogs, although the reason for this is not clear. These results indicate that the duration of action of YM020 is shorter than that of omeprazole in rats and dogs and that YM020 may induce the release of less gastrin than omeprazole. This finding suggests the possibility that YM020 does not produce hyperplasia.

In general, antisecretory agents inhibit gastric and duodenal lesions in rats (e.g. water-immersion restraint stress-, indomethacin-, cysteamine-induced lesions), and antiulcer potency closely depends on the antisecretory potency. In contrast, necrotizing agent (e.g. hydrochloric acid, ethanol)-induced gastric lesions are not suppressed by the inhibition of acid secretion, but rather by cytoprotective effects. It was reported that oral omeprazole protected gastric mucosa against absolute ethanol, but that intravenous injection of the drug was not protective (22). However, SCH 28080 has been reported to inhibit ethanol-induced gastric lesions in both oral and intravenous treatment (14, 15), indicating that SCH 28080 exerts a cytoprotective effect via a mechanism different from that of omeprazole. In the present study, omeprazole produced cytoprotection on oral dosing only, whereas YM020 showed this effect in both oral and subcutaneous administration. These results suggest that YM020, like SCH 28080, may have a cytoprotective effect via a mechanism different to that of omeprazole.

In conclusion, YM020 which inhibits H$^+$.K$^+$.ATPase via the competitive inhibition at the K$^+$-site, suppressed gastric acid secretion in rats and dogs. The recovery of acid secretion was more rapid with YM020 than with omeprazole. YM020 also suppressed the gastric and duodenal lesions induced by several ulcerogens. Furthermore, the protective effect of YM020 against absolute ethanol and 0.7 N HCl appeared to act via a different mechanism to that of omeprazole.

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