

## Antisecretory Effects of a Novel and Long-Lasting Histamine H<sub>2</sub>-Receptor Antagonist, YM-14471, in Rats and Dogs

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**ABSTRACT**—We investigated some properties of YM-14471 (2-2-[2-(diaminomethyleneamino)thiazol-4-yl]methylthio}ethyl-5-[3-(diethylamino)propyl]-6-methyl-pyrimidine-4-one trihydrochloride), a new H<sub>2</sub>-receptor antagonist, in comparison with those of famotidine, cimetidine and omeprazole. In guinea pig atria, famotidine and cimetidine produced a competitive dose-dependent displacement of histamine-induced tachycardia. In contrast, low concentrations of YM-14471 showed competitive inhibition of tachycardia, whereas high concentrations were irreversible or slowly dissociable. In pylorus-ligated rats, intravenous YM-14471, famotidine and cimetidine dose-dependently inhibited basal gastric secretion with ED<sub>50</sub> values of 0.04, 0.43 and 31.2 mg/kg, respectively. ED<sub>50</sub> values for oral YM-14471, famotidine, cimetidine and omeprazole were 0.81, 0.42, 28.9 and 7.7 mg/kg when given at 1 hr before ligation, and 5.7, 26.7, 1639.5 and 18.6 mg/kg at 5 hr before ligation. In anesthetized dogs, intravenous YM-14471, famotidine, cimetidine and omeprazole also dose-dependently inhibited histamine (160 μg/kg·hr)-induced acid secretion with ED<sub>50</sub> values of 13.7, 8.7, 333.3 and 65.3 μg/kg, respectively. In Heidenhain pouch dogs, YM-14471 inhibited histamine (40 μg/kg·hr)-induced acid secretion by both intravenous (0.02 mg/kg) and oral administration (0.3 mg/kg). Moreover, the inhibitory effect of YM-14471 was more prolonged than those of famotidine and cimetidine by either route, and it was as long as that of omeprazole dosed orally. These results suggest that YM-14471 is an irreversible or slowly dissociable H<sub>2</sub>-receptor antagonist, and has long antisecretory effect.

**Keywords:** YM-14471, Histamine H<sub>2</sub>-receptor antagonist (novel), Gastric acid secretion, Famotidine, Cimetidine

Before the development of histamine H<sub>2</sub>-receptor antagonists, large numbers of surgical procedures for gastric and duodenal peptic ulcers were performed, and antacid was used to neutralize gastric acid. The development of cimetidine, an H<sub>2</sub>-receptor antagonist, has resulted in a decrease in the number of operations for gastric and duodenal ulcers (1). To achieve similar results with antacids to those for H<sub>2</sub>-receptor antagonists, they must be given in very large doses and at great frequency. The considerable therapeutic success of H<sub>2</sub>-receptor antagonists may be ascribed to their promotion of healing, rapid relief of symptoms and good patient compliance. Subsequent to cimetidine came the development of ranitidine (2) and famotidine (3, 4), both more effective H<sub>2</sub>-receptor antagonists than cimetidine, providing confirmation of the high potency and safety of this class of compound in clinical use.

Omeprazole irreversibly inhibits the proton pump, which is the terminal step in acid secretion, and it has potent and long-acting antisecretory effects *in vitro* (5) and *in vivo* (6). In humans, omeprazole in a single dose of 20–40 mg/kg induces the complete abolition of intragastric acidity throughout a 24-hr period (7), and it produces a better rate of healing in ulcer disease (8) than famotidine (3, 4), ranitidine (2) and cimetidine (9, 10). This superior potency of omeprazole in clinical use may be due to the longer duration of its antisecretory effects as compared with the H<sub>2</sub>-receptor antagonists.

We recently discovered a new H<sub>2</sub>-receptor antagonist, YM-14471 (Fig. 1). In the present study, we investigated the histamine H<sub>2</sub>-receptor blocking activity of this compound in isolated guinea pig right atria and its antisecretory activity in rats and dogs, and compared the results with those of famotidine, cimetidine and omeprazole.

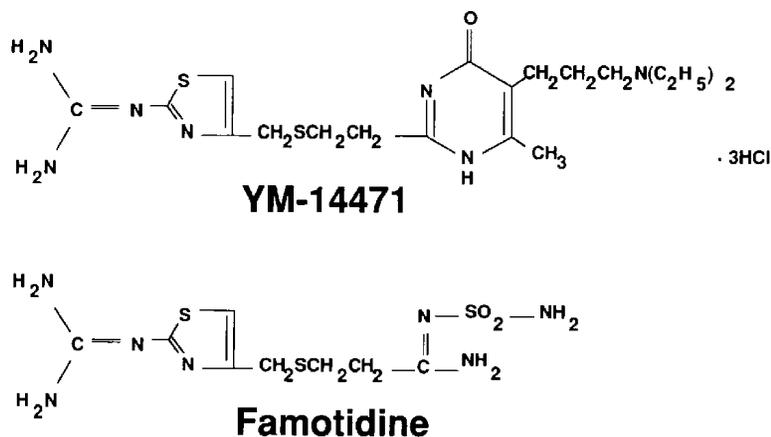


Fig. 1. Chemical structures of YM-14471 and famotidine.

## MATERIALS AND METHODS

### *Chronotropic studies in guinea pig right atria*

Histamine  $H_2$ -receptor antagonistic properties were determined in guinea pig right atria. Male Hartley guinea pigs weighing 450–700 g were killed by bleeding. The right atria were dissected *in situ*, freed of connective tissue, and mounted at 1-g tension in a 10-ml tissue bath containing oxygenated Krebs-Henseleit solution (95%  $O_2$ , 5%  $CO_2$ ) at 37°C. The composition of Krebs-Henseleit solution was: 118.4 mM NaCl, 4.7 mM KCl, 1.2 mM  $MgSO_4$ , 2.5 mM  $CaCl_2$ , 11.1 mM dextrose, 25.0 mM  $NaHCO_3$  and 1.2 mM  $KH_2PO_4$ , dissolved in distilled and demineralized water. The tissues were attached to isometric force transducers (TB-611T; Nihon Kohden Co., Tokyo) connected to an ink oscillograph (MC6621; Graphtec, Tokyo) through carrier amplifiers (AP-621G, Nihon Kohden) and a cardiometer (AT-601G, Nihon Kohden). Equilibration was undertaken for 1 hr before the addition of drugs. After submaximum positive chronotropic responses in the spontaneously beating right atria were obtained, cumulative histamine or isoproterenol concentration-response curves were constructed by increasing the bath concentration of the agonist by approximately 3-fold gradations. Test compound was added to the bath 30 min before rechallenge with histamine or isoproterenol.

Reversibility of the histamine-induced tachycardia was investigated after washout of the bath containing YM-14471. After construction of the histamine concentration-response curve, YM-14471 was added to the bath, followed 30 min later by washout of the bath with fresh Krebs-Henseleit solution 3 times. Histamine concentration-response curves were reconstructed 10 min later and every 60 min thereafter.

### *Basal acid secretion in pylorus-ligated rats*

Male Wistar rats weighing 200–250 g were used. They were fasted 18 hr prior to the experiment with free access to water. Under ether anesthesia, the abdomen was incised and the pylorus ligated. They were then placed in individual mesh cages to prevent coprophagy. Four hours later, the animals were killed with ether and the gastric contents 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 were intravenously injected immediately after ligation or orally administered 1 or 5 hr before ligation.

### *Gastric acid secretion in anesthetized dogs*

Mongrel dogs of both sexes weighing 10–15 kg were used after fasting for 18 hr with free access to water. They were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and maintained by intravenous infusion at 3 mg/kg·hr. 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 given intravenously after gastric secretion induced by histamine (160  $\mu$ g/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*

Male beagle dogs weighing 7 to 12 kg were used. A Heidenhain pouch was prepared by the conventional method under anesthesia with a combination of nitrous oxide, oxygen and halothane. Beginning 1 month after preparation of the pouch, secretory tests were performed once a week throughout the experiments. The animals were fasted with free access to water for 18 hr before the

experiments. 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 was infused intravenously via a cannulae incubated in the hind limb. In most cases, histamine (40 µg/kg·hr)-induced gastric acid secretion reached a steady state at 2 or 3 hr after the start of infusion.

Drug doses were determined from preliminary experiments in which doses producing approximately 70% to 80% maximum inhibition of secretory responses to histamine over 15 min were determined. Drugs were given intravenously or orally after gastric secretion induced by histamine (40 µg/kg·hr) reached a steady state.

To determine the duration of the inhibitory effect of YM-14471, we examined the effect of histamine on acid secretion at 24 hr after oral pretreatment of YM-14471. YM-14471 (0.3 mg/kg) was dosed orally; and 21 hr later, histamine (40 µg/kg·hr) intravenous infusion was started, and the steady state acid output induced by histamine was measured. Data were compared with the steady state acid output in an untreated group.

#### Statistical evaluation

In *in vitro* studies, the dose-ratio was obtained from the ratio of EC<sub>50</sub> values of an agonist in the presence and absence of an antagonist. K<sub>B</sub> values were determined at each concentration of antagonist according to the following equation (11):

$$K_B = [\text{Antagonist, M}] / (\text{dose ratio} - 1)$$

The pA<sub>2</sub> values were then expressed as the negative logarithm of K<sub>B</sub>. In addition, the log (dose ratio - 1) was plotted against the log of the molar concentration of the antagonist, and the regression line and slope of the curve were calculated (12).

In *in vivo* studies, all values represent the mean ± S.E.M. Statistical significance was determined by analysis of variance. Probabilities of < 5% (P < 0.05) were considered significant. ED<sub>50</sub> values were determined by log-probit analysis from data obtained for three doses of each compound.

#### Drugs

YM-14471 (2-2-[2-(diaminomethyleneamino)thiazol-4-yl]methylthio}ethyl-5-[3-(diethylamino)propyl]-6-methylpyrimidine-4-one trihydrochloride), famotidine, cimetidine and omeprazole were prepared at Yamanouchi Pharmaceutical Co., Ltd.; and histamine dihydrochloride (Sigma, St. Louis, MO, USA) and isoproterenol (Nikken, Tokyo) were obtained commercially. In *in vitro* experiments, famotidine and cimetidine were dissolved in N/10 hydrochloric acid and diluted with Krebs-Henseleit solution, while the others were dissolved and diluted with Krebs-Henseleit solution. In *in vivo* experi-

ments, drugs given orally to rats were suspended in 0.5% methylcellulose solution. In Heidenhain pouch dog, drugs were filled into gelatin capsules and given orally with 5–10 ml of water. In experiments using intravenous injection, famotidine and cimetidine were dissolved in N/10 hydrochloric acid and diluted with 0.9% (w/v) sodium chloride solution (saline) with pH adjusted to 6.5–7.0, while YM-14471 was dissolved in saline. Omeprazole was dissolved in N/10 sodium hydroxide solution and diluted saline, with pH adjusted to 7.0–7.5. All drug doses are in terms of the free base.

## RESULTS

#### *Chronotropic studies in guinea pig right atria*

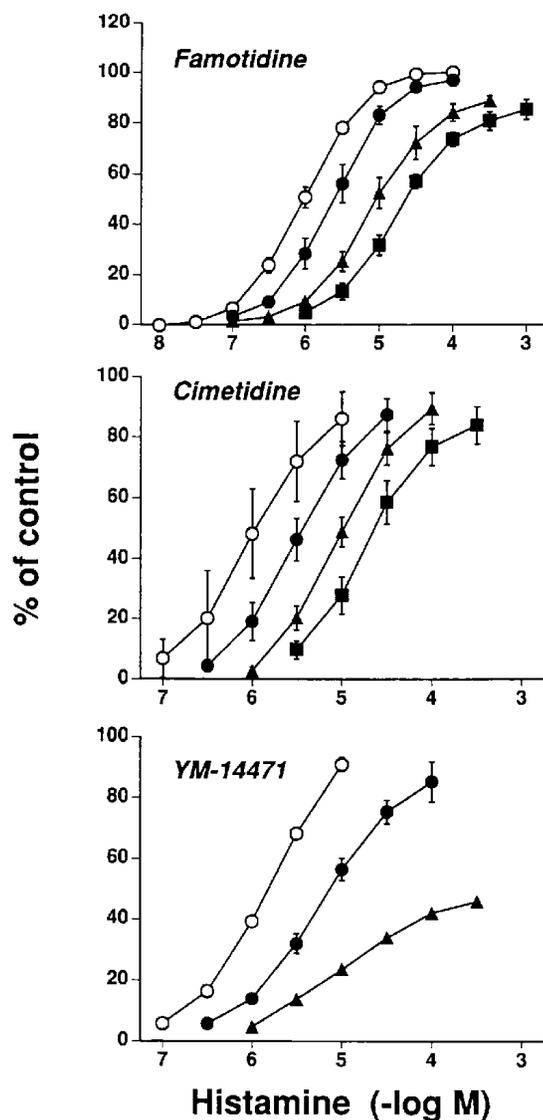
The resting rate of the guinea pig right atria was 192.1 ± 4.2 beats/min (n=44). Histamine (10<sup>-7</sup>–10<sup>-5</sup> M) induced a positive chronotropic effect in the atria. The EC<sub>50</sub> was 1.05 × 10<sup>-6</sup> M, and the maximum response was 145.7 ± 3.1 beats/min at 10<sup>-4</sup> M of histamine. Famotidine (3 × 10<sup>-8</sup>–3 × 10<sup>-7</sup> M) and cimetidine (3 × 10<sup>-6</sup>–3 × 10<sup>-5</sup> M) produced a dose-related displacement of the histamine concentration-response curves without significantly affecting their "slope" or maximum response, with pA<sub>2</sub> values of 7.7 and 6.4, respectively. YM-14471 (10<sup>-7</sup> M) shifted the histamine concentration-response curve to the right without affecting the maximum response to histamine with a pA<sub>2</sub> value of 7.8, whereas at 3 × 10<sup>-7</sup> M, it shifted the histamine concentration-response curve to the right and also decreased the maximum response to histamine (Fig. 2).

To investigate the mode of action of YM-14471, we examined the reversibility of the response to histamine after washout of the bath containing YM-14471. The increase in atrial rate induced by histamine was not reversed 6 hr after washout of YM-14471 from the tissue bath (data not shown).

Isoproterenol (10<sup>-9</sup>–3 × 10<sup>-7</sup> M) induced a positive chronotropic effect in guinea pig right atria. The EC<sub>50</sub> value was 1.81 × 10<sup>-8</sup> M, and the maximum response was 120.5 ± 3.0 beats/min at 3 × 10<sup>-7</sup> M. YM-14471 had no effect on the isoproterenol concentration-response curve; the EC<sub>50</sub> value of isoproterenol with 3 × 10<sup>-7</sup> M of YM-14471 was 1.79 × 10<sup>-8</sup> M, and the maximum response to isoproterenol was 97.4 ± 4.6% of the control.

#### *Basal acid secretion in pylorus-ligated rats*

Basal acid output was 203.7 ± 27.5 µEq over 4 hr in pylorus-ligated rats (n=20). Intravenous injection of YM-14471 (0.01–0.1 mg/kg), famotidine (0.3–3 mg/kg) and cimetidine (10–100 mg/kg) dose-dependently inhibited basal acid secretion (Fig. 3), with ED<sub>50</sub> values of 0.04, 0.43 and 31.2 mg/kg, respectively (Table 1).

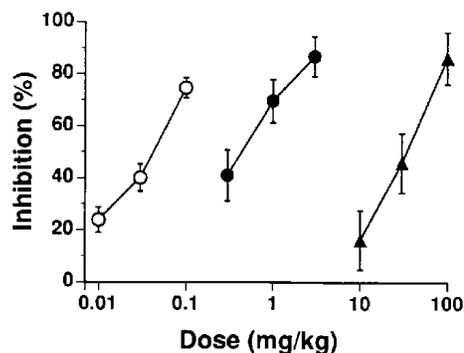


**Fig. 2.** Inhibitory effects of famotidine, cimetidine and YM-14471 on histamine-induced tachycardia in guinea pig right atria. Famotidine (○: control, ●:  $3 \times 10^{-8}$  M, ▲:  $10^{-7}$  M, ■:  $3 \times 10^{-7}$  M) and cimetidine (○: control, ●:  $3 \times 10^{-6}$  M, ▲:  $10^{-5}$  M, ■:  $3 \times 10^{-5}$  M) dose-dependently inhibited the chronotropic effect of histamine in a competitive manner. YM-14471 (○: control, ●:  $10^{-7}$  M, ▲:  $3 \times 10^{-7}$  M) showed noncompetitive inhibition. Each curve is the mean obtained from 4 atria.

Oral administration of YM-14471, famotidine, cimetidine and omeprazole also dose-dependently suppressed basal acid secretion at doses of 0.3–3, 0.3–3, 10–100 and 10–30 mg/kg on 1-hr pretreatment before ligation and at 3–30, 10–100, 300–3000 and 10–100 mg/kg on 5-hr pretreatment, respectively (Fig. 4).  $ED_{50}$  values are shown in Table 1.

#### Gastric acid secretion in anesthetized dogs

YM-14471 (0.003–0.03 mg/kg), famotidine (0.003–



**Fig. 3.** Effects of intravenous injection of YM-14471 (○), famotidine (●) and cimetidine (▲) on basal acid secretion in pylorus-ligated rats. Each value represents the mean  $\pm$  S.E. of 10 animals.

**Table 1.**  $ED_{50}$  values of YM-14471, famotidine, cimetidine and omeprazole on pylorus-ligated rats and anesthetized dogs

Drugs	$ED_{50}$			
	Pylorus-ligated rat (mg/kg)			Anesthetized dog ( $\mu$ g/kg)
	i.v.	p.o.		i.v.
		1 hr <sup>*)</sup>	5 hr <sup>*)</sup>	
YM-14471	0.04	0.81	5.7	13.7
Famotidine	0.43	0.42	26.7	8.7
Cimetidine	31.2	28.9	1639.5	333.3
Omeprazole	— <sup>**)</sup>	7.7	18.6	65.3

<sup>\*)</sup>: In pylorus-ligated rats, the drugs were given orally 1 or 5 hr before the pylorus ligation. <sup>\*\*)</sup>: Not tested.

0.03 mg/kg), cimetidine (0.1–1 mg/kg) and omeprazole (0.03–0.3 mg/kg) on intravenous administration inhibited histamine ( $160 \mu$ g/kg·hr)-induced acid secretion in a dose-dependent manner (Fig. 5).  $ED_{50}$  values are listed in Table 1. Based on these data, YM-14471 was approximately 24 and 5 times more potent than cimetidine and omeprazole, respectively, and comparable to famotidine.

#### Gastric acid secretion in Heidenhain pouch dogs

Intravenous injection of YM-14471 (0.02 mg/kg), famotidine (0.02 mg/kg) and cimetidine (0.5 mg/kg) significantly inhibited histamine ( $40 \mu$ g/kg·hr)-induced acid secretion. Doses which produced 70% to 80% maximum inhibition over 15 min in preliminary experiments were used. Inhibition of secretion began 0.5 hr after injection for all drugs. The inhibitory effect of YM-14471 lasted 4 hr after injection, whereas those of famotidine and cimetidine disappeared at 3.5 and 2 hr after injection, respectively (Fig. 6).

Oral administration of YM-14471 (0.3 mg/kg), famoti-

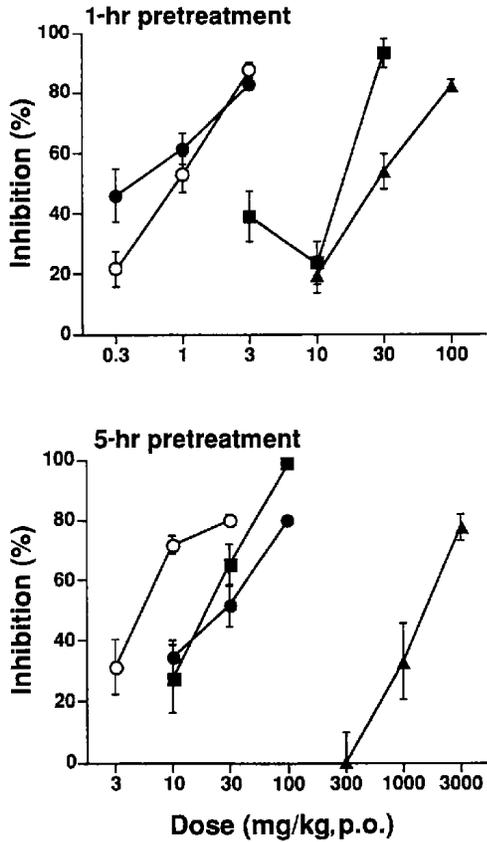


Fig. 4. Effects of oral treatment of YM-14471 (○), famotidine (●), cimetidine (▲) and omeprazole (■) on basal acid secretion in pylorus-ligated rats. Each value represents the mean ± S.E. of 10 animals.

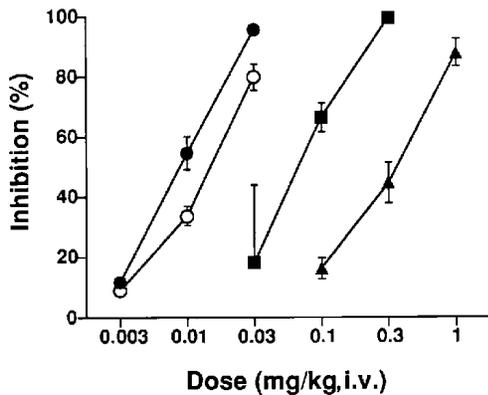


Fig. 5. Inhibitory effects of YM-14471 (○), famotidine (●), cimetidine (▲) and omeprazole (■) on histamine (160 μg/kg·hr)-induced acid secretion in anesthetized dogs. Each value represents the mean ± S.E. of 3 or 4 animals.

dine (0.03 mg/kg) and cimetidine (3 mg/kg) also inhibited acid secretion induced by histamine (40 μg/kg·hr). Doses which produced 70% to 80% maximum inhibition

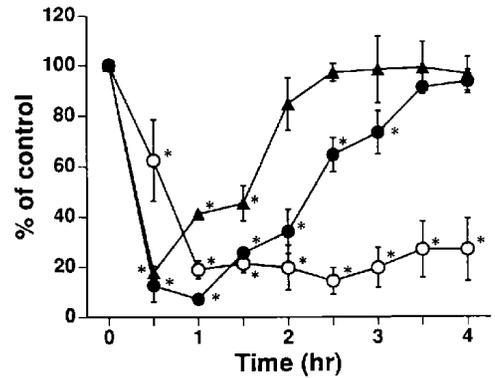


Fig. 6. Time course of inhibitory effects of intravenous YM-14471 (○: 0.02 mg/kg), famotidine (●: 0.02 mg/kg) and cimetidine (▲: 0.5 mg/kg) on histamine (40 μg/kg·hr)-induced acid secretion in Heidenhain pouch dogs. Each value represents the mean ± S.E. of 3 or 4 animals. Drugs were administered after histamine-induced acid secretion had reached a steady state. \*: P < 0.05 (vs. acid output just before the treatment of drugs).

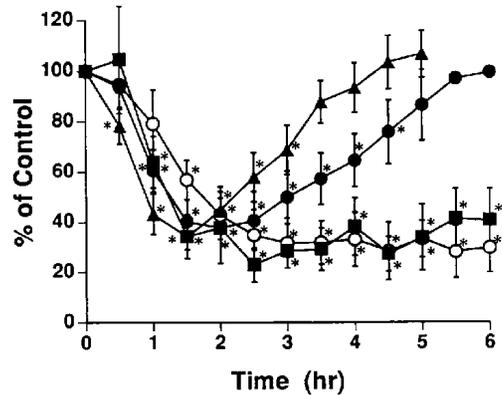


Fig. 7. Time course of inhibitory effects of oral YM-14471 (○: 0.3 mg/kg), famotidine (●: 0.03 mg/kg), cimetidine (▲: 3 mg/kg) and omeprazole (■: 3 mg/kg) on histamine (40 μg/kg·hr)-induced acid secretion in Heidenhain pouch dogs. Each value represents the mean ± S.E. of 3 or 4 animals. Drugs were administered after histamine-induced acid secretion had reached a steady state. \*: P < 0.05 (vs. acid output just before the treatment of drugs).

over 15 min in preliminary experiments were used. Cimetidine began to suppress acid secretion at 0.5 hr after treatment, and famotidine and omeprazole began to suppress it at 1 hr. YM-14471 suppressed acid secretion significantly at 1.5 hr after treatment and produced 70% inhibition at 6 hr. Inhibitory effects of famotidine and cimetidine disappeared at 5 and 3.5 hr after treatment, respectively (Fig. 7). Omeprazole (3 mg/kg) inhibited acid secretion by 60% at 6 hr after treatment, indicating that the duration of the antisecretory effect of omeprazole was similar to that of YM-14471 (Fig. 7).

To determine the duration of action of YM-14471, histamine-induced acid secretion was measured at 24 hr after oral administration of the compound. Acid output induced by histamine at 24 hr after pretreatment with YM-14471 was not significantly different from that in the untreated group, indicating that the antisecretory effect of YM-14471 disappeared no later than 24 hr after oral administration (data not shown).

## DISCUSSION

The present studies were carried out to characterize and evaluate the antisecretory properties of YM-14471 in animal models in comparison with the histamine H<sub>2</sub>-receptor antagonists famotidine and cimetidine and the H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor omeprazole.

In isolated guinea pig atria, a low concentration of YM-14471 shifted the histamine concentration-response curve to the right without changing the maximum response to histamine. YM-14471 had no effect on the isoproterenol concentration-response curve. These results, as well as its structural similarity to famotidine, indicate that YM-14471 has no non-specific inhibitory effect on atrial rate, and may like famotidine and cimetidine have histamine H<sub>2</sub>-receptor blocking activity. The degree of displacement of the histamine concentration-response curve to the right by YM-14471 at 10<sup>-7</sup> M was closely similar to that by the same concentration of famotidine, indicating that the affinity of YM-14471 was as potent as that of famotidine. Famotidine and cimetidine produced a concentration-dependent displacement of the histamine concentration-response curve to the right without changing the maximal response, but a high concentration of YM-14471 both shifted the curve and suppressed the maximum response, suggesting that the receptor blockade of famotidine and cimetidine are competitive, whereas that of YM-14471 is not. This unsurmountable antagonism by YM-14471 is due to its irreversibility or slow dissociation, as evidenced by its antagonism continuing for 6 hr after washout of the bath.

In pylorus-ligated rats, YM-14471 inhibited basal acid secretion by both intravenous and oral administration. The antisecretory activity of YM-14471 was approximately 11 times more potent than that of famotidine when dosed intravenously, but was 2 times less potent when dosed orally 1 hr prior to ligation. Judging from the oral-to-intravenous ED<sub>50</sub> ratio, YM-14471 may not be as well absorbed from the gastrointestinal tract as famotidine or a significant percentage of oral YM-14471 may undergo first pass metabolism in the liver.

In contrast to these findings, YM-14471 was more potent than the other drugs in the inhibition of basal acid secretion when given orally 5 hr before pylorus ligation.

To evaluate the duration of the antisecretory effects of the test compounds, ED<sub>50</sub> values obtained with the pretreatment times of 1 and 5 hr were compared. The ED<sub>50</sub> (5 hr) to ED<sub>50</sub> (1 hr) ratio for oral YM-14471 was 7, a value not as good as that for omeprazole (=2), but much smaller than those for famotidine (=64) and cimetidine (=57). These results indicate that YM-14471, although slightly inferior to omeprazole, is a long-acting antisecretory agent in pylorus-ligated rats.

In anesthetized dogs, the inhibitory effect of intravenous YM-14471 on histamine-induced acid secretion was approximately 2 times less potent than that of famotidine. It is not clear why the antisecretory ranking of YM-14471 and famotidine here was different from that in pylorus-ligated rats, but one reason is that not only histaminergic but also cholinergic and gastrinergic stimulation contribute to basal gastric acid secretion in the pylorus-ligated rat. In addition, we also consider this difference in ranking to be probably caused by the difference in the duration of their antisecretory action. The potency of test compounds in anesthetized dogs was compared with ED<sub>50</sub> values as calculated from the degree of maximal inhibition based on gastric secretion over 15 min. In contrast, potency in pylorus-ligated rats was compared with ED<sub>50</sub> values calculated from inhibition of gastric secretion over 4 hr. Thus, the duration of the antisecretory action was not taken into consideration for ED<sub>50</sub> values in anesthetized dogs, which may have contributed to the difference in the antisecretory ranking of YM-14471 and famotidine between rats and dogs.

In conscious dogs with Heidenhain pouches, YM-14471 showed a long-lasting antisecretory effect on both intravenous and oral administration. The ranking of antisecretory duration was YM-14471 > famotidine > cimetidine when the drugs were dosed intravenously and YM-14471 = omeprazole > famotidine > cimetidine when the drugs were dosed orally. These rankings in Heidenhain pouch dogs were roughly consistent with the results obtained with pylorus-ligated rats. The difference in antisecretory duration between YM-14471 and famotidine or cimetidine may reflect the above-mentioned difference in their mode of histamine H<sub>2</sub>-receptor antagonism, that is, competitive antagonism (famotidine and cimetidine) versus irreversible or slow dissociation (YM-14471).

It is well known that omeprazole, a proton pump inhibitor, has potent antisecretory effects both *in vitro* (5) and *in vivo* (6). In humans, omeprazole in a single daily dose of 20–40 mg completely abolishes intragastric acidity throughout a 24 hr period (7); and it produces better healing of acid-related diseases (8) than cimetidine (9, 10), ranitidine (2) and famotidine (3, 4). In the present study, omeprazole inhibited basal secretion in pylorus-ligated rats and histamine-induced gastric acid secretion in

Heidenhain pouch dogs for a much longer period than famotidine and cimetidine. In these *in vivo* systems, YM-14471 also showed long-lasting antisecretory effects, and at smaller doses than omeprazole. From these results, YM-14471, like omeprazole, is expected to show more potent antisecretory and antiulcer activity than famotidine and cimetidine in clinical use.

In summary, YM-14471 is an irreversible or slowly dissociable histamine H<sub>2</sub>-receptor antagonist. The antisecretory activity of this compound is longer than that of famotidine by both intravenous and oral administration.

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