Pharmacological Profiles of a New Antiulcer Agent, SWR-215

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We investigated the effects of a new antiulcer agent, SWR-215 ([(1,2-dihydro-2-oxo-4-quinolinyl)methyl]thio]-N-[[4-(1-piperidinylmethyl)-2-pyridinyl]oxy]-Z-2-butenyl]acetamide, on histamine H₂-receptors, gastric acid secretion and various acute experimental gastric lesions. SWR-215 showed unsurmountable histamine H₂-antagonism on isolated guinea-pig atrium. In gastric secretion studies, SWR-215 exhibited potent and durable inhibitory effects, and the antisecretory activities were much stronger than that of roxatidine acetate hydrochloride (roxatidine): 5 times stronger on basal acid secretion in pylorus ligated rats, 11 times stronger on histamine-stimulated acid secretion in acetic fistula rats, and 2 times stronger on histamine-stimulated acid secretion in Heidenhain-pouch dogs, respectively. In various experimental acute gastric lesion studies, SWR-215 potentially inhibited almost all acute gastric and duodenal lesions compared with roxatidine, especially indomethacin-induced and HCl-ethanol-induced gastric lesions, and the inhibitory effects were exhibited at the same or lower doses than those which caused the antisecretory effect. Furthermore, it was considered that the mucosal protective effect of SWR-215 was probably unrelated to the endogenous prostaglandin system in gastric mucosa.

These results suggest that SWR-215 possesses both durable antisecretory and mucosal protective effects, and is expected to be a useful drug for the treatment of patients with peptic ulcers.

Key words SWR-215; histamine H₂-receptor antagonist; gastric acid secretion; mucosal protective effect; roxatidine acetate hydrochloride

It is generally accepted that peptic ulcers are caused by a loss in the balance of aggressive factors (i.e., acid and pepsin) and mucosal defensive factors (i.e., mucus, bicarbonate secretion and mucosal blood flow). In current therapy for the healing of an ulcer, antisecretory drugs, such as histamine H₂-receptor antagonists or proton pump inhibitors, have been shown to reduce or regulate the gastric acid secretion, thereby showing marked therapeutic effects. However, to sustain the healing or to prevent a relapse of the ulcer, prostaglandins (PGs) as potent cytoprotective agents and other mucosal protective drugs have been combined with antisecretory drugs. Although the cytoprotective mechanisms of PGs have not been clarified, the protective effect provided by these agents are generally attributed to an increase in gastric mucosal defense factors.¹

For histamine H₂-receptor antagonism, it was believed that an imidazole ring and a cyanoguanidine or nitro-ethendiamine element in the side chain were essential.² However, cimetidine that is included in both essential structures showed some clinically relevant side effects, such as antiandrogenic effects, interference with drug-metabolizing enzymes in the liver, and mental confusion.³,⁴ Subsequently, histamine H₂-receptor antagonists with new configurations such as ranitidine, famotidine and roxatidine acetate (Fig. 1) have been synthesized to improve their efficacy and specificity at the H₂-receptor and to elicit fewer or no side effects. In these compounds, the imidazole ring has been replaced by a furan, thiazole, or benzene ring, and the guanidine moiety has been modified to increase the antiulcer activity and decrease side effects. On the other hand, 2(1H)-quinolinone derivatives have been developed as β-adrenergic blockers,⁵ β-adrenergic stimulants⁶ and/or antiulcer drugs.⁷ Among them we were interested in the antiulcer drug, rebamipide (Fig. 1), as it was reported that the compound was known to promote the healing of acetic acid-induced gastric ulcer and to prevent the recurrence and/or relapse of chronic gastric ulcers in rats without inhibiting acid secretion.⁸ Therefore, we were interested in synthesizing the aromatic ring and flexible alkyl chain prepared from well-known histamine H₂-receptor antagonists combined with 2(1H)-quinolinone.

In our search for an H₂-receptor antagonist that exerts both antisecretory and cytoprotective activities, we have found a novel anti ulcer agent, [(1,2-dihydro-2-oxo-4-quinolinyl)methyl]thio]-N-[[4-(1-piperidinylmethyl)-2-pyridinyl]oxy]-Z-2-butenyl]acetamide (SWR-215, Fig. 1), among the various derivatives containing quinolinone in their structure. In the present study, the effects of SWR-215

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Fig. 1. Chemical Structure of SWR-215, Rebamipide and Roxatidine Acetate
on histamine H$_2$-receptors in isolated guinea-pig atria, gastrointestinal secretion in rats and dogs and ulceration in rat stomachs and duodenums were investigated, and the effects were compared with those of roxatidine acetate hydrochloride (Fig. 1).

**MATERIALS AND METHODS**

**Experimental Animals** Male Hartley guinea-pigs (Japan SLC, Hamamatsu, Japan), male Sprague-Dawley rats and male Donryu rats (Charles River Japan, Inc., Yokohama, Japan), and male and female beagle dogs (BMR, Gifu, Japan) were used in the present study. The animals were housed in an animal room at 23 ± 2°C and 55 ± 10% relative humidity, and were given free access to food and tap water.

**Chemicals** Histamine dihydrochloride (histamine), indomethacin, Tween 80 and carboxymethyl cellulose (CMC) were purchased from Wako Pure Chemicals (Osaka, Japan). Mepirizole (Mebron G$^\text{®}$) was obtained from Daichi (Tokyo, Japan). SWR-215 and roxatidine acetate hydrochloride (roxatidine) as a reference drug, were synthesized in our laboratory.

**Histamine H$_2$-Receptor Antagonistic Activity** Male Hartley guinea-pigs (250—440 g) were killed by a blow on the head and the whole heart was excised and immersed in oxygenated Krebs-Henseleit solution. The right atrium was dissected away from the rest of the heart, and immediately suspended in a 15-mL Magnus chamber filled with Krebs-Henseleit solution. 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$_2$PO$_4$, dissolved in distilled and demineralized water. The incubation medium was warmed at 31 ± 1°C and continuously bubbled with a 95% O$_2$—5% CO$_2$ gas mixture. The atrial preparations were subjected to an 0.8-g resting tension and allowed to stabilize for about 60 min. Measurements of the amplitude of contraction and the beat rate were conducted using an isometric force transducer (TB651T) and a cardiograph (AT601G, Nihon Kohden, Tokyo, Japan), respectively. Histamine (10$^{-8}$—10$^{-4}$ M) was added to the chamber in a cumulative fashion using the 1/2 log interval, then the concentration—response curve was obtained as a control, and the curve was recorded with a chart recorder (WT685G, Nihon Kohden, Tokyo, Japan). Subsequently, solutions of the drugs were added 10 min prior to the next histamine cumulation. The drugs were dissolved in Krebs-Henseleit solution to 10$^{-5}$ M and diluted before use. The pA$_2$ values and the slope were determined by the Schild plots method.$^{10}$

**Gastric Acid Secretion in Rats** Male Sprague-Dawley rats (180—220 g) were fasted with free access to water for 18 h prior to the experiments. The rats were placed in individual stainless steel cages with a raised mesh-bottom to prevent coprophagy. Drugs were suspended or dissolved in 0.5% CMC solution.

Basal Secretion: Under ether anesthesia, the abdomen of each rat was incised and the pylorus ligated. After the incision was closed, the animals were placed in cages with a raised mesh-bottom to prevent coprophagy. Four hours after the pylorus ligation the animals were killed, and the gastric contents were collected and analyzed. The acidity was determined by titrating 0.1 ml of the gastric contents with 0.1 N NaOH to pH 7.0 with a potentiometric automatic titrator (AT-400, Kyoto Electronics, Kyoto, Japan). The total acid output was expressed as μeq·h$^{-1}$. Drugs or the vehicle alone were administered intraduodenally (i.d., 2.5 ml/kg) at 0.5 h before the ligation.

**Stimulated Secretion** An acute gastric fistula was prepared in each rat according to the methods of Okabe et al.$^{11}$ Under ether anesthesia, the abdomen was opened and a polyethylene cannula (fistula tube) was placed in the forestomach to collect gastric juice. Another small polyethylene cannula was inserted in the proximal duodenum through the pylorus to inject drugs, and then the pylorus was ligated together with the small cannula. Both cannulas were brought out and the incision was closed. After recovery from the anesthesia, the animals were placed in Bollman cages (Natsume, Tokyo, Japan). Histamine dissolved in saline was infused continuously (8 mg·kg$^{-1}$·h$^{-1}$) via the tail vein at the rate of 1.2 ml/h. Gastric juice was collected from the fistula tube at 1-h intervals for 4 h and the volume (ml) was measured. The acidity was determined according to the procedure described in the basal secretion study. The acid output was expressed as μeq·h$^{-1}$. Drugs or the vehicle alone were administered i.d. at a volume of 2.5 ml/kg 0.5 h prior to the start of the infusion.

**Stimulated Gastric Acid Secretion in Dogs** Both male and female beagle dogs (8—13 kg) were used in this experiment. A Heidenhain-pouch was prepared in each dog according to the method of Robert et al.$^{12}$ The pouch was prepared at least 2 months before the secretory test. The animals were fasted with free access to water for 18 h before the secretory test. Gastric juice was drained through an implanted stainless cannula. After twice obtaining the basal 15-min gastric juice collection, histamine dissolved in saline was infused continuously (160 μg·kg$^{-1}$·h$^{-1}$) via the saphena vein at the rate of 10 ml/h. After the start of infusion, gastric juice was collected at 15-min intervals for 3 h, and the volume and acidity were analyzed according to the procedure described in the rat gastric secretion study. The acid output was expressed as μeq/15 min.$^{13}$ Secretory studies were performed once weekly on each dog. SWR-215 was dissolved in a minimal amount of 0.1 N HCl solution, then diluted with saline (final pH 5). Roxatidine was dissolved in saline. Each drug or the vehicle was administered intravenously (i.v.) 1 h after the start of histamine infusion.

**Acute Gastric and Duodenal Lesions** Male Sprague-Dawley rats (180—220 g) were used in the experiments of water immersion stress- and HCl-ethanol-induced gastric lesions. Male Donryu rats (190—230 g) were used in the experiments of indomethacin-induced and 1.5% NH$_4$-induced gastric lesions, and rats of the same species (330—370 g) were used in the mepirizole-induced duodenal lesion study. The rats were fasted for 18 h prior to the experiments, with free access to water. During the fasting, the rats were placed in cages with a raised mesh-bottom to prevent coprophagy. Drugs were suspended or dissolved in 0.5% CMC solution. Drugs or the vehicle alone were administered orally at a volume of 5 ml/kg.
Water Immersion Stress-Induced Gastric Lesions: Rats were fixed in a Tohda-yakusaku type stress cage (Natsume, Tokyo, Japan), then immersed to the depth of the xiphoid in a water bath (23°C). After 7 h of stress, the animals were killed; their stomachs were excised and inflated by injecting 10 ml of 1% formalin, then immersed in 1% formalin for 10 min to lightly fix the gastric or duodenal wall. The stomachs were then incised along the greater curvature and the mucosal lesions in the glandular portion were examined.14 Drugs or the vehicle alone were administered orally 5 min before the water immersion.

Indomethacin-Induced Gastric Lesions: Indomethacin suspended in the saline with a minimal amount of Tween 80, was given subcutaneously to rats at 30 mg/kg. Seven hours later, the animals were killed with ether, then their stomachs were examined for lesions.15 Drugs or the vehicle alone were administered orally 0.5 h before the indomethacin treatment.

HCl-Ethanol-Induced Gastric Lesions: HCl-ethanol (60% ethanol, 150 mm HCl) was given orally to rats at a volume of 1 ml/rat. One hour later, the animals were killed with ether and their stomachs were removed. After formalin treatment, each stomach was examined for lesions.16 Drugs or the vehicle alone were administered orally 0.5 h before the administration of HCl-ethanol.

1.5% NH₃-Induced Gastric Lesions: 1.5% NH₃ was given orally to rats at a volume of 1 ml/rat. One hour later, the animals were killed with ether and the stomach was removed from each animal. After formalin treatment, each stomach was examined for lesions. Drugs or the vehicle alone were administered orally 0.5 h before the administration of 1.5% NH₃.

Mepirizole-Induced Duodenal Lesions: Mepirizole suspended in 0.5% CMC solution was given orally to rats at 250 mg/kg. Twenty four hours later, the animals were killed with ether and the stomach and duodenum was removed from each animal.17 After formalin treatment, each duodenum was examined for lesions. Drugs or the vehicle alone were administered orally 0.5 before and 8 h after the mepirizole treatment.

Effect of Endogenous PGs on HCl-Ethanol-Induced Gastric Lesions: To investigate the participation of endogenous PGs on the cytoprotective effect of SWR-215, the following experiment was carried out according to the method of Robert et al.18 Briefly, the HCl-ethanol-induced gastric lesion study was performed with or without indomethacin pretreatment (5 mg/kg, s.c.) 1.5 h before the administration of HCl-ethanol. SWR-215 or 20% ethanol was given orally 0.5 h before the administration of HCl-ethanol.

Determination of Gastric or Duodenal Lesions: The length (mm) of the gastric lesion or the area (mm²) of duodenal lesion was measured under a dissecting microscope (Olympus, Tokyo, Japan) with a square grid (×10), and the sum of lesions per stomach or duodenum was used as the lesion index.

Statistical Analysis of Data Data were expressed as mean ± S.E. Statistical differences were determined by Dunnett’s test for unpaired observation following one-way analysis of variance, or by a paired t-test. The p value of statistically significant differences was set at p < 0.05. The ED₅₀ or IC₅₀ values were calculated by the Litchfield and Wilcoxon method.

RESULTS

Effects on Histamine H₂-Receptor In guinea-pig right atria, accumulated histamine at 10⁻⁸ to 10⁻⁴ M increased the beating rate in a concentration-dependent manner, and the basal beating rate reached about 250 beats/min. Ten min pretreatment with SWR-215 (10⁻⁷ to 3 × 10⁻⁷ M) inhibited the histamine-induced positive chronotropic response. The dose-response curve of histamine was shifted to the right with depression of the maximum response level, as the addition dose of SWR-215 was increased (Fig. 2). The IC₅₀ value of SWR-215 was

<table>
<thead>
<tr>
<th>Compound</th>
<th>pA₂</th>
<th>Slope of Schild plot</th>
<th>IC₅₀ (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWR-215</td>
<td></td>
<td></td>
<td>1.37 × 10⁻⁷</td>
</tr>
<tr>
<td>Roxatidine</td>
<td>7.27</td>
<td>1.00</td>
<td>2.21 × 10⁻⁷</td>
</tr>
</tbody>
</table>

The IC₅₀ value was obtained from the response to 3 × 10⁻⁸ M histamine.

![Fig. 2. Effects of SWR-215 and Roxatidine on Histamine-Induced Chronotropic Response in Isolated Guinea-Pig Atria](image-url)

Values represent the mean ± S.E.
Table 2. Effects of Intraduodenally Administered SWR-215 and Roxatidine on Basal Gastric Secretion in Pylorus-Ligated Rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>No. of rats</th>
<th>Total volume (ml/4 h)</th>
<th>Inhibition (%)</th>
<th>Total acid output (μeq/4 h)</th>
<th>Inhibition (%)</th>
<th>ED_{50} (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWR-215</td>
<td>Control</td>
<td>12</td>
<td>6.1 ± 0.6</td>
<td>21.3</td>
<td>562 ± 79</td>
<td>29.9</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>9</td>
<td>4.8 ± 0.4</td>
<td>34.4</td>
<td>394 ± 60</td>
<td>52.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>10</td>
<td>4.0 ± 0.4*</td>
<td>27.9</td>
<td>265 ± 49*</td>
<td>50.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9</td>
<td>4.4 ± 0.4*</td>
<td>55.7</td>
<td>277 ± 38*</td>
<td>76.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>8</td>
<td>2.7 ± 0.4*</td>
<td>82.8</td>
<td>130 ± 29*</td>
<td>76.9</td>
<td></td>
</tr>
<tr>
<td>Roxatidine</td>
<td>Control</td>
<td>10</td>
<td>53.3 ± 0.4</td>
<td>28.3</td>
<td>449 ± 64</td>
<td>34.6</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9</td>
<td>3.8 ± 0.3*</td>
<td>34.0</td>
<td>294 ± 39*</td>
<td>56.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>10</td>
<td>3.5 ± 0.3*</td>
<td>37.7</td>
<td>196 ± 33*</td>
<td>75.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>10</td>
<td>3.3 ± 0.4*</td>
<td></td>
<td>110 ± 26*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each drug was given intraduodenally 0.5 h before the ligation. Control rats were given the vehicle alone. Animals were killed 4 h after the ligation. Values represent the mean ± S.E. Significantly different from the control group: *p < 0.05.

Table 3. Effects of SWR-215 and Roxatidine on Histamine-Stimulated Gastric Secretion in Acute Fistula Rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>No. of rats</th>
<th>Total volume (ml/4 h)</th>
<th>Inhibition (%)</th>
<th>Total acid output (μeq/4 h)</th>
<th>Inhibition (%)</th>
<th>ED_{50} (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWR-215</td>
<td>Control</td>
<td>8</td>
<td>10.6 ± 0.5</td>
<td>8.5</td>
<td>1404 ± 90</td>
<td>14.5</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
<td>9.7 ± 0.6</td>
<td>36.8</td>
<td>1201 ± 115</td>
<td>44.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>6.7 ± 1.3*</td>
<td>73.6</td>
<td>779 ± 190*</td>
<td>91.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
<td>2.8 ± 0.5*</td>
<td>2.9</td>
<td>122 ± 41*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roxatidine</td>
<td>Control</td>
<td>8</td>
<td>10.5 ± 0.9</td>
<td>2.9</td>
<td>1393 ± 175</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>10.2 ± 1.2</td>
<td>21.0</td>
<td>1031 ± 136</td>
<td>28.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6</td>
<td>8.3 ± 0.7</td>
<td>28.6</td>
<td>887 ± 76*</td>
<td>38.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>6</td>
<td>7.5 ± 0.5</td>
<td>51.4</td>
<td>313 ± 90*</td>
<td>78.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>5</td>
<td>5.1 ± 0.7*</td>
<td></td>
<td>313 ± 90*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each drug was administered intraduodenally 0.5 h before the start of histamine infusion. Control rats were given the vehicle alone. Each value represents the mean ± S.E. as the total acid output for 4 h after the start of infusion. Significantly different from the control group: *p < 0.05.

1.37 × 10^{-7} M. Roxatidine (10^{-7}-10^{-5} M) antagonized the histamine response and parallel-shifted the dose-response curve of histamine to the right without depressing the maximum response to histamine. The pA_{2} and IC_{50} values for roxatidine were 7.27 and 2.21 × 10^{-7} M, respectively.

Effects on Gastric Secretion in Rats

Basal secretion: Four hours after the pylorus ligation, the volume of the gastric contents and acid output in the control group was about 6 ml and 500 μeq/h, respectively. When SWR-215 was administered intraduodenally at 3—30 mg/kg, the volume and acid output significantly decreased, in a dose-dependent manner (Table 2). Roxatidine also significantly decreased these parameters at 10—100 mg/kg. The ED_{50} values for SWR-215 and roxatidine were 4.3 and 22.5 mg/kg, respectively.

Histamine-Stimulated Secretion: The basal acid secretion before the start of histamine infusion was 70 μeq/h (n = 8). When the histamine was infused continuously at 8 mg/kg/h via the tail vein, acid output reached a maximum of about 400 μeq/h for 1—2 h in the control group (Fig. 3). Intraduodenal administration of SWR-215 at 3 and 10 mg/kg 0.5 h before the histamine significantly inhibited the stimulated secretion in dose-dependent manner, and the inhibitory effect was maintained for 4 h. Roxatidine at 10—30 mg/kg also significantly inhibited gastric secretion, but the inhibitory effect disappeared by 4 h. In the case of expression per the total volume (ml/4 h) and total acid output (μeq/4 h), SWR-215 at 10 mg/kg inhibited them 73.6% and 91.3%, respectively, whereas roxatidine at 100 mg/kg inhibited them 51.4% and 78.2%, respectively (Table 3). ED_{50} values of SWR-215 and roxatidine...
for the total acid output were 3.1 and 34.7 mg/kg, respectively.

Effect on Stimulated Gastric Acid Secretion in Dogs As the histamine was continuously infused, it gradually stimulated gastric acid secretion, which reached a maximum secretion level of about 0.6—0.8 meq/15 min at 60 min. At 60 min after the start of histamine infusion, the intravenous administration of SWR-215 at 0.3 and 1.0 mg/kg was effective on the stimulated gastric secretion, significantly and potentially, for 120 min after injection, but at the dose of 0.1 mg/kg it had little effect (Fig. 4). The time of the maximum inhibitory effect was about 30 min after drug injection. Roxatidine at 0.1 mg/kg had no effect, but at 0.3 and 1.0 mg/kg, it caused dose-dependent and significant inhibition (Fig. 4). The onset time of inhibition was 30 min after the drug treatment and the inhibitory effect gradually decreased after 60 min. The ED_{50} values of SWR-215 and roxatidine for total acid output for 120 min after the drug administration were 0.20 and 0.44 mg/kg, respectively (Table 4).

Effect on Acute Gastric and Duodenal Lesions The effects of SWR-215 and roxatidine on various experimental lesions are shown in Fig. 5.

Water Immersion Stress-Induced Gastric Lesions: Water immersion stress for 7 h induced multiple mucosal lesions, mainly in the corpus area, with 100% incidence. The lesion index in the control group was 18.6 ± 2.5 mm. Five min before immersion, the oral administration of SWR-215 at 3, 10 and 30 mg/kg significantly prevented the appearance of stress-induced lesions. Roxatidine was significantly effective at doses of 30 and 100 mg/kg, but it had a little effect at less than 10 mg/kg. The ED_{50} values for SWR-215 and roxatidine were 7.9 and 18.7 mg/kg, respectively.

Indomethacin-Induced Gastric Lesions: Seven hours after the subcutaneous administration of indomethacin at 30 mg/kg, similar mucosal lesions induced by water immersion stress were observed in the corpus area and, infrequently, in the antrum. The lesion index in the control group was 27.4 ± 4.8 mm. SWR-215, administered orally 0.5 h before the indomethacin treatment, prevented mucosal lesions dose-dependently and remarkably at doses in the range of 1—30 mg/kg; the inhibition ratio at 30 mg/kg was 100%. Roxatidine at <60 mg/kg had little effect, however, at 100 mg/kg it had a high inhibition ratio (80.6%). The ED_{50} values for SWR-215 and roxatidine were 0.9 and 76.4 mg/kg, respectively.

HCl—Ethanol-Induced Gastric Lesions: HCl—ethanol, as a necrotizing agent that was administered orally, formed severe gastric mucosal lesions after 1 h. The lesion index in the control group was 74.1 ± 6.7 mm. SWR-215 given orally 0.5 h before the administration of HCl—ethanol showed significant inhibitory effects at doses in the range of 3—30 mg/kg. Roxatidine was effective at higher doses (30—100 mg/kg). The ED_{50} values for SWR-215 and roxatidine were 3.2 and 53.7 mg/kg, respectively.

1.5% NH_{3}-Induced Gastric Lesions: 1.5% NH_{3} also formed severe mucosal lesions resembling those induced

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**Table 4. Comparison of Antisecretory and Antiulcer Activity of SWR-215 and Roxatidine Based on ED_{50} Values**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Route</th>
<th>SWR-215 (mg/kg)</th>
<th>Roxatidine (mg/kg)</th>
<th>Ratio Roxatidine/SWR-215</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric acid secretion (rat)</td>
<td>i.d.</td>
<td>4.3</td>
<td>22.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Basal secretion</td>
<td>i.d.</td>
<td>3.1</td>
<td>34.7</td>
<td>11.2</td>
</tr>
<tr>
<td>Gastric acid secretion (dog)</td>
<td>i.v.</td>
<td>0.20</td>
<td>0.44</td>
<td>2.2</td>
</tr>
<tr>
<td>Histamine-stimulated-secretion</td>
<td></td>
<td>7.9</td>
<td>18.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>p.o.</td>
<td>9.0</td>
<td>76.4</td>
<td>84.9</td>
</tr>
<tr>
<td>HCl—ethanol</td>
<td>p.o.</td>
<td>3.2</td>
<td>53.7</td>
<td>16.8</td>
</tr>
<tr>
<td>1.5% NH_{3}</td>
<td>p.o.</td>
<td>3.3</td>
<td>4.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Duodenal ulcer (rat)</td>
<td>p.o.</td>
<td>3.4</td>
<td>6.3</td>
<td>1.9</td>
</tr>
</tbody>
</table>

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Fig. 4. Effects of SWR-215 and Roxatidine on Histamine-Stimulated Gastric Secretion in Heidenhain-Pouch Dogs

Each drug was administered i.v. 1 h after the start of infusion. Control rats were given the vehicle alone. Each point represents the mean ± S.E. of 3 animals. Significantly different from the control group: *p < 0.05.
by HCl-ethanol. The lesion index in the control group was 76.1 ± 9.6 mm. SWR-215 and roxatidine given orally 0.5 h before the administration of 1.5% NH₃ showed significant and dose-dependent inhibition effects at a dose range of 3–30 mg/kg; both drugs had almost the same inhibitory effect on gastric lesion formation. The ED₅₀ values for these drugs were 3.3 and 4.9 mg/kg, respectively.

Mepirizole-Induced Duodenal Lesions: Mepirizole (250 mg/kg, p.o.) induced one or two penetrating ulcers in the proximal part of the duodenum 24 h after oral administration. The ulcer index in the control group was 7.1 ± 1.4 mm². SWR-215 and roxatidine, given orally 0.5 h before and 8 h after the administration of mepirizole, prevented the formation of duodenal ulcers, and these inhibitory effects were significant at doses higher than 10 mg/kg. The ED₅₀ values for these drugs were 3.4 and 6.3 mg/kg, respectively.

Effect of Endogenous PGs on HCl-Ethanol-Induced Gastric Lesions: The administration of SWR-215 (10 mg/kg) and 20% ethanol almost completely inhibited HCl-ethanol-induced gastric lesions (Fig. 6). On the other hand, when pretreated with indomethacin subcutaneously 1 h before administration of the drug or 20% ethanol, the inhibitory activity of 20% ethanol completely disappeared, while that of SWR-215 still remained.

Comparison of Antisecretory and Antiulcer Action The ED₅₀ values for SWR-215 and roxatidine on basal- or stimulated-gastric secretion and various kinds of experimental ulcers are summarized in Table 4. The gastric secretion study revealed that the antisecretory potency of SWR-215 was about 3 to 9 times higher than that of roxatidine. SWR-215 exhibited about twice as strong an effect as roxatidine against stress-induced lesions and against 1.5% NH₃-induced gastric lesions, about 17 times stronger effect on HCl-ethanol-induced lesions, and an 85 times stronger effect on indomethacin-induced gastric lesions. In addition, SWR-215 was shown to be about 2 times more potent than roxatidine on duodenal ulcers.

DISCUSSION

The present study demonstrated that SWR-215 possessed not only a more potent antisecretory effect than previously used drugs, but also antiulcer effects with defensive factors.

The study of guinea-pig isolated atria showed that the effects of a high concentration of SWR-215 could not be overcome completely by increasing the concentration of histamine. This form of noncompetitive inhibition, termed "unsurmountable antagonism" by Gaddum et al.,¹⁹ was consistent with the findings of other investigators.₂₀,₂¹ In addition, SWR-215 seems to bind tightly to the receptor site since the inhibitory action of SWR-215 persisted after
repeated washings of the tissue. Its inhibition profile was the same as that of other new-type histamine H3-receptor antagonists, such as IT-066 or FRG-8813,23,24 and was different from classic histamine H2-receptor antagonists, such as cimetidine. The potency of the antagonistic activity of SWR-215 based on the IC50 value was approximately 2 times greater than that of roxatidine. The apparent high affinity of SWR-215 for the histamine H2-receptor and the noncompetitive and/or unsurmountable nature of the antagonism may account for the extensive duration of its gastric antisecretory action \textit{in vivo}.

Concerning the antisecretory effects, in the pylorus-ligated rat, intraduodenally administered SWR-215 intensely inhibited the basal secretion. Comparison of the ED50 values showed that the activity ratio of SWR-215 was about 5 times higher than that of roxatidine. SWR-215 administered by the same route exhibited more profound inhibitory effects on secretions stimulated by the continuous infusion of histamine, and the effects persisted for longer than 4 h. The inhibitory effect of SWR-215 on the ED50 value, determined by the total acid output for 4 h, was about 11 times higher than that of roxatidine. Furthermore, a similarly potent and persistent inhibitory effect of SWR-215 given intravenously was obtained in the histamine-stimulated secretion study of dogs, in which the potency was found to be approximately 2 times stronger than that of roxatidine. The difference in the antisecretory activity ratio between rats and dogs was considered to reflect differences in the administration route and species.24–26] Famotidine, which is reported to be an unsurmountable histamine H2-receptor antagonist,27 has an antagonistic action similar to that of SWR-215. The long-acting antisecretory effects of famotidine were attributed to the fact that the interaction with the histamine H2-receptor was by slow dissociation and/or irreversible. In addition, it was reported that a compound containing a piperidinomethyl pyridinyl group, instead of a pipericinomethylphenyl group, had potent and long-acting antisecretory effects. It was suggested that the differences in antisecretory effects between SWR-215 and roxatidine were attributed to those unique structural groups of the aromatic ring. Therefore, the interaction mode between SWR-215 and the histamine H2-receptor, a factor of persistent antisecretory effect, should be evaluated. On the other hand, the antisecretory activity of SWR-215 was also observed for other secretagogues, \textit{i.e.} carbachol and pentagastrin, in rats. Intraduodenal administration of SWR-215 at 10 mg/kg more effectively inhibited acid secretion by histamine than by carbachol or pentagastrin, as shown by the inhibition of total acid output (data not shown). These results suggest that SWR-215 indirectly inhibited acid secretion stimulated by carbachol or pentagastrin.

In acute gastric and duodenal lesions, SWR-215 showed the same or stronger inhibitory effects as roxatidine against all five experimental gastric lesions. Against water immersion stress-induced gastric lesions and meperidole-induced duodenal ulcers, the antiulcer effects of SWR-215 and roxatidine were closely correlated to their antisecretory effects. In the pathogenesis of these two experimental lesions or ulcers, gastric acid was considered to play a major role, because antacid and antisecretory drugs were able to reduce the lesion or ulcer.28–31] However, SWR-215 was found to be most effective against indomethacin-induced and HCI–ethanol induced- gastric lesions compared to the other lesions. The potency of the effects of SWR-215 against the two lesions based on ED50 values were, respectively, about 90 and 17 times higher than that of roxatidine. The cytoprotective doses of roxatidine were apparently different from its antisecretory doses. It was suggested that the cytoprotective action of roxatidine was caused by the antisecretory action. Indomethacin, a non-steroidal anti-inflammatory drug (NSAID), administered at 30 mg/kg, reduced endogenous prostaglandins, thereby acting as a defensive factor in the gastric mucosa.32] Regarding the pathogenesis of indomethacin-induced lesions, Ueki et al.33] have suggested the acceleration of gastric motility and a reduction of mucosal blood flow, as a mucosal defensive factor induced the gastric lesions. Against indomethacin-induced lesions, SWR-215 showed high cytoprotective activity, about 4 times higher than its antisecretory effect, and had no effect on basal or indomethacin-accelerated gastric hypermotility (data not shown). The pathogenesis of HCl–ethanol induced gastric lesions was considered to include a reduction of various defensive factors based on the disturbance of mucosal blood flow,34 regardless of the influence on gastric acid secretion. SWR-215 showed a potent cytoprotective activity at the same dose as it showed an antisecretory effect; moreover, this effect did not include an increase in endogenous prostaglandins. Although the mechanisms of cytoprotection by SWR-215 are unknown, an increase in gastric mucosal blood flow was observed (data not shown). This effect may be partially responsible for the mechanisms of cytoprotection. These results suggest that SWR-215 has not only antisecretory activity, but also properties that increase some gastric mucosal defensive factors, such as gastric mucosal blood flow, bicarbonate secretion and mucous, thereby contributing to its antiulcer effect.

With regard to the structure, rebamipide, possessing a 2(1H)-quinolone structure, was selected through a drug-screening system by assessing the curative effects against an acetic acid-induced gastric ulcer, a typical model of a chronic experimental ulcer. This drug was also demonstrated to be effective against various acute experimental ulcer models, especially necrotizing agent-induced gastric ulcers, caused by depleting gastric mucosa.35] SWR-215 also has a 2(1H)-quinolone skeleton in its structure. A potent cytoprotective activity of SWR-215 may be associated with its moiety.

In conclusion, the findings of the present study suggested that the new antiulcer agent, SWR-215, possesses both highly persistent antisecretory effects and a mucosal protective effect, and may be a useful drug for the treatment of patients with peptic ulcers.

Further studies are in progress to clarify the pharmacological actions of SWR-215.

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