The Relationship of Intraduodenal pH and Delayed Gastric Emptying in Duodenal Ulceration Induced by Mepirizole or Cysteamine in Rats

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Abstract—Subcutaneous administration of mepirizole (60 and 200 mg/kg) and cysteamine (100 and 300 mg/kg) to fasted rats consistently induced localized villous damage to the proximal duodenum after 6 to 8 hr. The severity of the damage in animals treated with the low doses remained unchanged at 12 hr. With the high doses, however, well-defined deep ulcers were evident by that time, the incidence being high. The agents caused a significant accumulation of highly acidic gastric contents for 6 to 8 hr, but the accumulated gastric contents had markedly decreased by 12 hr. The intraduodenal pH in these animals was significantly lowered for 8 hr with the low doses, but for 12 hr with the high doses. Both mepirizole and cysteamine significantly delayed gastric emptying which was quantitated by weighing the food residue in refed animals. This delay in emptying was observed for 6 to 8 hr with the low doses and for 12 hr with the high doses. We conclude that this prolonged accumulation of gastric contents for up to 8 hr, resulting in a continuous lowering of the intraduodenal pH for 12 hr, is a crucial factor for the progression from duodenal villous damage to visible ulcers in response to mepirizole and cysteamine.

Both mepirizole and cysteamine induce penetrating ulcers in the proximal duodenum of rats within 24 hr of oral or parenteral administration in a dose-dependent manner (1–4). The mechanism of the ulcerogenicity of these agents was investigated by several investigators (5–9), but it remains unclear. We recently found that the villous damage in the duodenum was first evident at 1 hr after subcutaneous administration of mepirizole at 200 mg/kg (ulcerogenic dose) and cysteamine at 100 mg/kg (non-ulcerogenic dose) (10). The degree of the initial damage, i.e., exposure of the lamina propria, was much the same with the two treatments. Interestingly, the two duodenal ulcerogens had caused marked accumulation of acidic gastric contents and significant lowering of the intraduodenal pH by that time. These functional changes appear to be causally related to the villous damage; i.e., corrosive gastric contents emptied into the duodenum, most probably by

intraluminal and/or intraabdominal pressure, might damage the villi.

Therefore, this study was performed to determine whether the accumulation of gastric contents and the lowering of intraduodenal pH persist for up to 12 hr, which is the earliest time for visible ulcer formation (1, 11). We also wanted to investigate whether delayed gastric emptying and the decrease in duodenal pH contribute to the progression of early cellular damage to tissue damage in the proximal duodenum.

Materials and Methods

Male Sprague-Dawley rats, weighing 220–250 g (Nihon Charles-River, Atsugi, Japan), were fasted, but allowed free access to tap water, for 24 hr before the experiments. Water was withheld for only 2 hr before the experiments. The rats were kept in raised mesh bottom cages to prevent coprophagy. Each study was carried out with 8 animals per

group.

Induction of duodenal damage: To reconfirm the duodenal ulceration by mepirizole and cysteamine-HCl, the agents were administered subcutaneously into the backs of animals at 60 and 200 mg/kg and at 100 and 300 mg/kg, respectively. Animals were killed after 6, 8 and 12 hr, and the stomach and duodenum were removed as a single unit. Animals treated with the vehicle alone were killed 6 hr later and the stomach and duodenum were removed. After being opened along the greater curvature and the anti-mesenteric side, these organs were quickly extended on a glass sheet with the aid of a liquid adhesive (Aron Alpha, Toa Gosei Kagaku, Tokyo). The samples were gently washed with ice-cold saline and then put into 5% paraformaldehyde-4% glutaraldehyde in phosphate buffer (pH 7.4) for 1 hr at 4°C. Subsequently, the damaged area (mm²) of the duodenal mucosa was quickly determined under a dissecting microscope ($\times 10$). The person (S.O.) measuring the lesions did not know the treatment given to the animals. The samples were again put into the above fixative for 2 hr at 4°C and then postfixed in 1% OsO₄ for 1 hr. After fixation and dehydration through a graded series of ethanol solutions, the tissues were subjected to critical point drying with CO₂ (HLP-2; Hitachi, Ibaraki), mounted and then vacuum-coated with a palladium-platinum ion sputter (IB-3; Eicho, Ibaraki). The samples were then examined for damage under a scanning electron microscope (S-510; Hitachi, Ibaraki). The entire duodenum was scanned, and the area showing the most severe damage was recorded for indexing. The severity of the damage (damage index) was divided into five degrees, as follows:

- 0: normal duodenal mucosa
- 1: epithelial cell damage as defined by destruction of cell membrane on the duodenal villous tips
- 2: exfoliation of epithelial cells and exposure of the lamina propria
- 3: low and broad villi due to destruction of the lamina propria
- 4: penetration of the damage through the muscularis mucosa (ulceration)

Gastric contents and intraduodenal pH:

Mepirizole (60 and 200 mg/kg), cysteamine (100 and 300 mg/kg) or the vehicle alone was administered subcutaneously; and the animals were killed after 1, 2, 4, 6, 8 and 12 hr. The abdomen was incised along the linea alba, and the stomach and duodenum were exposed. The lower end of the esophagus and the pylorus were immediately clamped to avoid any leakage of gastric contents. The duodenum was opened along the anti-mesenteric side, and then the end of a pH test paper (Toyo Roshi, Tokyo, Japan) was placed lightly on the luminal surface of the proximal duodenum for 3 sec. Determination of the intraduodenal pH was performed in duplicate. The stomach was then removed and the gastric contents were collected in graduated test tubes. Gastric samples were centrifuged at 3,000 rpm for 10 min, and then the volume and acidity were determined. Titratable acidity was determined by automatic titration with 0.1 N NaOH to pH 7.0, using an autoburette (ABU 80; Radiometer, Copenhagen). The amount of acid was calculated by multiplying the acidity and the volume of each sample, and it was expressed as $\mu\text{Eq/stomach}$.

Gastric emptying: After 24 hr fasting, the animals were given food and water freely for 1 hr. Subsequently, food and water again withheld, and the animals were killed immediately or after 1, 2, 4, 6, 8 and 12 hr. The stomachs were removed, and the gastric contents were collected in test tubes and then centrifuged at 3,000 rpm for 15 min. The total weight (g) of the gastric contents and the weight (g) of the juice were determined. Mepirizole (60 and 200 mg/kg), cysteamine (100 and 300 mg/kg) or the vehicle alone was administered subcutaneously when the refeeding was complete.

Drugs: Mepirizole (Daiichi, Tokyo, Japan) and cysteamine-HCl (Sigma, St. Louis, MO) were suspended in 0.5% carboxymethylcellulose and administered in a volume of 1 ml/200 g body wt.

Statistics: Data are expressed as means $\pm$ S.E. The mean values were compared using the unpaired Student's *t*-test, and $P < 0.05$ was regarded as being significant.

Results

Induction of duodenal damage: The animals

all tolerated mepirizole and cysteamine for up to 12 hr. No animals in the control groups showed visible damage to the proximal duodenum. Six to eight hours after administration of 60 or 200 mg/kg of mepirizole, one or two superficial damages were observed on the anterior and/or posterior wall of the duodenum under a dissecting microscope (Fig. 1A). The same degree of duodenal damage was observed at 6 to 8 hr after treatment with 300 mg/kg of cysteamine, but not with 100 mg/kg of the agent. Twelve hours later, the degree of damage evident with 60 mg/kg of mepirizole was much the same as that observed at 6 or 8 hr. However, a well-defined, deep ulcer developed in all animals

treated with 200 mg/kg of mepirizole (mean damaged area, 17.8 ± 4.4 mm²). Animals treated with 300 mg/kg, but not with 100 mg/kg, of cysteamine also had visible duodenal ulcers at 12 hr, the incidence being 87.5% (mean damaged area, 10.0 ± 3.6 mm²).

Scanning electron microscopic examination revealed that most of the villi in the proximal duodenum of the control animals were intact. However, mepirizole administered at 60 and 200 mg/kg, and cysteamine at 300 mg/kg induced severe villous damage, the degree being the same at 6 and 8 hr (Fig. 1B). The damage induced with 100 mg/kg of cysteamine was less severe compared with the lesions caused with 300 mg/kg of the

Fig. 1. Duodenal mucosal damage in rats induced by subcutaneously administered mepirizole (MZ) and cysteamine (CA) at 6, 8 and 12 hr. The degree of damage was determined by either gross (A) or scanning electron microscopic (B) observation. Note that the damaged area markedly increased from 8 to 12 hr. Eight animals were used for each group. * and Δ: significant difference from the control and between the two doses at $P < 0.05$, respectively. Values are means $\pm$ 1 S.E.

same agent. At 12 hr, the damage induced with 60 mg/kg of mepirizole was less severe compared with that observed at 6 and 8 hr. However, the lesions produced by 200 mg/kg of mepirizole and 100 and 300 mg/kg of cysteamine were much the same as those observed at 6 and 8 hr.

Gastric contents: In the 24-hr fasted control animals, there were little or no gastric contents. When mepirizole was administered at 60 mg/kg, there was a significant accumulation of gastric juice (the volume and amount of acid being 1.7 ± 0.3 ml/stomach and 170.9 ± 33.5 μ Eq/stomach, respectively) at 1 hr (Fig. 2). Such accumulation persisted for

8 hr. However, the volume and amount of acid had significantly decreased by 12 hr, i.e., the values were 0.4 ± 0.1 ml/stomach and 26.6 ± 10.1 μ Eq/stomach (vs. 1.8 ± 0.3 ml/stomach and 213.4 ± 38.5 μ Eq/stomach at 8 hr), respectively. With 200 mg/kg, the volume and amount of acid gradually increased with time, the maximal values being reached at 6 hr. The values were 2.9 ± 0.3 ml/stomach and 374.8 ± 36.7 μ Eq/stomach; i.e., significantly higher than those observed with 60 mg/kg. The same degree of accumulation was observed even at 8 hr. At 12 hr, however, the gastric contents were greatly reduced toward control levels, as observed with 60 mg/kg.

Fig. 2. Time-course and dose-response studies on the effect of subcutaneously administered mepirizole (MZ) on the accumulation of gastric contents in rats. At various times, animals were killed, and the volume of the gastric contents was determined. Note that the accumulated gastric contents reached the maximal level at 6 hr, but had markedly decreased by 12 hr. * and Δ : significant difference from the control levels or between the two doses at $P < 0.05$, respectively. Eight animals were used for each study. Values are means $\pm$ 1 S.E.

When cysteamine was administered at 100 mg/kg, there was a marked accumulation of gastric juice at 1 hr, the volume and amount of acid being 2.3 ± 0.2 ml/stomach and 204.0 ± 25.3 μ Eq/stomach, respectively (Fig. 3). These values were maximum at 6 hr (4.3 ± 0.5 ml/stomach and 488.8 ± 59.4 μ Eq/stomach). Interestingly, there was no accumulation of gastric juice at 8 and 12 hr. In contrast to the low dose, 300 mg/kg of cysteamine caused gradual increases in the volume, from 0.8 ± 0.1 ml/stomach at 1 hr to 6.0 ± 0.5 ml/stomach at 6 hr, and the amount of acid, from 55.8 ± 3.6 μ Eq/stomach at 1 hr to 703.4 ± 56.1 μ Eq/stomach at 6 hr. The accumulation of gastric contents then began to decrease with time. At 12 hr, the volume and

amount of acid had decreased to 0.7 ± 0.2 ml/stomach and 92.9 ± 22.8 μ Eq/stomach, respectively. These reductions were significantly different from those at 8 hr.

Intraduodenal pH: In the control groups, the intraduodenal pH was around 6.8 for 12 hr (Fig. 4). Both mepirizole and cysteamine, regardless of the dose, significantly lowered the intraduodenal pH for 8 hr. However, the pH in animals treated with 100 mg/kg of cysteamine at 8 hr was 5.4 ± 0.3 . The intraduodenal pH at 12 hr after administration of 60 mg/kg of mepirizole and 100 mg/kg of cysteamine was nearly at control levels. However, the pH in the animals administered 200 mg/kg of mepirizole and 300 mg/kg of cysteamine remained low; i.e., 3.3 ± 0.4 and

Fig. 3. Time-course and dose-response studies on the effect of subcutaneously administered cysteamine (CA) on the accumulation of gastric contents in rats. At various times, animals were killed, and the volume of the gastric contents was determined. Note that the accumulated gastric contents reached the maximal level at 6 hr, but had markedly decreased by 8 and 12 hr with 100 mg/kg, and by 12 hr with 300 mg/kg. * and Δ : significant difference from the control levels or between the two doses at $P < 0.05$, respectively. Eight animals were used for each group. Values are means $\pm$ 1 S.E.

Fig. 4. Time-course and dose-response studies on the effects of subcutaneously administered mepirizole (MZ) and cysteamine (CA) on the intraduodenal pH in rats. The intraduodenal pH, decreased with the low doses, had returned to the control range by 12 hr, yet with the high doses, it remained low, even at 12 hr. *: significantly different from the corresponding control levels at $P < 0.05$. Eight animals were used for each group. Values are means $\pm$ S.E.

3.6 ± 0.4 , respectively.

Gastric emptying: The stomachs of refed rats were filled with ingested food and water. The total gastric contents in the control animals were 9.2 ± 1.3 g/stomach, of which the liquid portion was 0.8 ± 0.2 g/stomach. One hour later, the contents were reduced, being 2.6 ± 0.3 g/stomach (Fig. 5). Most of the animals had negligible gastric contents thereafter. Pretreatment with mepirizole significantly delayed gastric emptying (Fig. 5A). With 60 mg/kg, the delay in emptying persisted for 8 hr after administration, but the contents had disappeared by 12 hr. The liquid portion of the gastric contents at 1, 2, 4, 6 and 8 hr was significantly larger than that at 0 hr (1.7 ± 0.2 , 2.3 ± 0.3 , 1.6 ± 0.2 , 2.4 ± 0.3 and 1.6 ± 0.3 g/stomach vs. 0.8 ± 0.2 g/stomach). With 200 mg/kg, the gastric emptying was markedly inhibited at 12 hr. The liquid portion at 1, 2 and 6 hr was significantly larger than that at 0 hr (1.7 ± 0.2 , 1.8 ± 0.2 and 2.9 ± 0.3 g/stomach vs. 0.8 ± 0.2 g/stomach). Pretreatment with cysteamine at either dose also significantly delayed gastric emptying for at least 8 hr (Fig. 5B). However, the extent of the delay in gastric emptying, particularly as to the solid contents, was less marked than that

with mepirizole. With 100 mg/kg, the liquid portion observed at 1, 2, 4 and 6 hr was significantly larger than that at 0 hr (2.8 ± 0.2 , 3.2 ± 0.2 , 2.4 ± 0.3 and 3.1 ± 0.3 g/stomach vs. 0.8 ± 0.2 g/stomach), suggesting the stimulation of gastric secretion by the agent. At 12 hr, there was no more accumulation of gastric contents with the low dose, but still significant accumulation with the high dose. With 300 mg/kg, the liquid portion was also significantly larger than that in the control group, even at 8 hr (2.6 ± 0.3 g/stomach vs. 0.8 ± 0.2 g/stomach).

Discussion

The present results confirmed our previous findings (2, 12) that both mepirizole administered at 60 and 200 mg/kg and cysteamine at 100 mg/kg consistently induce duodenal villous damage in rats after 6 hr. In addition, we newly found that the severity of villous damage or small visible (observed under a dissecting microscope) lesions induced with the low doses was the same for up to 12 hr. However, the injury induced with the high doses, 300 mg/kg in case of cysteamine, progressed into visible ulcers in 8–12 hr. This time course of mucosal damage ob-

Fig. 5. Time-course and dose-response studies on the effects of subcutaneously administered mepirizole (MZ) and cysteamine (CA) on gastric emptying in rats. Gastric emptying was quantitated by measuring the food residue in the stomach of rats which had been refed for 1 hr after 24-hr fasting. Note that gastric emptying was significantly delayed by both agents for 8 to 12 hr. Eight animals were used for each group. * and Δ : significant difference from the control levels and between the two doses, respectively. Values are means $\pm$ 1 S.E. of the total gastric contents (Blanks in the column represent the liquid portion).

served with the high dose of cysteamine is consistent with that reported by Robert et al. (4). They demonstrated that the incidence and severity of visible ulcers induced with 425 mg/kg of subcutaneous cysteamine markedly increased from 8 to 12 hr after administration. Therefore, it is certain that elucidation of functional changes during this critical period for ulceration will provide an insight into the ulcerogenic mechanism of the agents.

As expected from our previous findings (10), the two ulcerogens induced marked accumulation of gastric contents for up to 8 hr after administration. In general, it is known that the accumulation of gastric contents is due to the summation of delayed emptying

and either basal or stimulated gastric secretion. Several investigators (13–15) and we (16) reported that both cysteamine and mepirizole significantly delayed gastric emptying in rats. We also confirmed in this study that the two ulcerogens markedly delayed gastric emptying. Cysteamine at ulcerogenic doses significantly stimulated gastric secretion in rats for about 4 to 8 hr (17–19). In addition, we found that the liquid portion of the gastric contents observed in the emptying study was markedly increased for 6 to 8 hr, thereby supporting its secretagogue activity. In contrast to cysteamine, mepirizole administered subcutaneously at 60 and 200 mg/kg showed a biphasic reaction as to gastric

secretion in rats with an acute fistula (2). The volume was significantly reduced with both doses for 1 hr, but increased with 60 mg/kg or remained unchanged with 200 mg/kg thereafter. Similar to cysteamine, mepirizole at both doses significantly increased the liquid portion of the gastric contents for 6 hr. While this finding would suggest the stimulative activity of mepirizole, there is a possibility that distention of the stomach by over 7 g of solid contents per se might have stimulated the secretion. In addition, the liquid portion in the mepirizole-treated group was more or less smaller than that in the cysteamine-treated group. Therefore, the accumulation of gastric contents after mepirizole treatment, particularly with 200 mg/kg, might be due to the basal, but not stimulated, gastric secretion. In any event, the gastric content accumulation in response to the two ulcerogens appears to be caused by the combination of delayed emptying and gastric secretion (either basal or stimulated).

We proposed that gastric content accumulation due to the ulcerogens is pathologically related to the early villous damage to the duodenum (10). Accordingly, the following two questions could be asked. Do accumulation of gastric contents and lowering of the intraduodenal pH in response to the low doses disappear with time, thus preventing further hazardous influence on the damaged villi? Conversely, do the accumulated gastric contents and lowered intraduodenal pH in response to the high doses persist for a much longer time, which is enough for the progression of villous damage to ulcers?

First, it was found that the accumulation of gastric contents following administration of the low doses of mepirizole persisted for 8 hr, but the gastric contents had mostly disappeared by 12 hr. The intraduodenal pH remained low for 8 hr after mepirizole administration at the low dose, suggesting that a small amount of acidic gastric contents might be continuously pushed into the duodenum despite of the delayed emptying. Indeed, we already demonstrated that a dye given orally 1 hr after cysteamine and mepirizole treatments was observed at the end of the small intestine within 60 min (20). As relatively large amounts of gastric contents passed into

the duodenum from 8 to 12 hr, the intraduodenal pH was assumed to remain low, even at 12 hr. Unexpectedly, the pH had returned to the control range by that time. We demonstrated that mepirizole subcutaneously administered at 60 mg/kg significantly inhibited duodenal HCO_3^- secretion in rats in response to HCl stimulation (2). However, it is possible that the inhibitory effect was transient and so duodenal HCO_3^- was secreted in a sufficient amount to neutralize the inflowing gastric acid. Cysteamine administered at the low dose also induced significant accumulation of the gastric contents and lowered the intraduodenal pH for 6 hr. At 8 and 12 hr, however, there was no accumulation and the intraduodenal pH had increased toward the control range, suggesting that gastric acid secretion had ceased and the inflowing gastric contents had almost been completely neutralized by that time. The short duration of accumulation of gastric contents in the case of cysteamine and the recovery of acid neutralization capacity with both mepirizole and cysteamine may be why the villous damage induced by the low doses did not result in ulcer formation.

Secondly, the degrees of the accumulation of gastric contents with the high doses of the agents were significantly higher than those with the low doses at 6 and 8 hr. The duration of the accumulation was much the same with the two doses of mepirizole, but was significantly longer with the high dose of cysteamine. In contrast to with the low dose, the accumulation of gastric contents in response to the high dose of cysteamine gradually increased, the maximum being reached at 6 hr. Since a delay in gastric emptying was already evident 1 hr after administration, this gradual accumulation appears to be due to the gradual stimulation of gastric acid secretion, as reported by other authors (21). The maximal volume and amount of acid with the high dose of cysteamine were almost double those with the high dose of mepirizole. At 8 hr, however, the volume and amount of acid were much the same between the two groups. This will be why the two agents induced nearly the same degree of ulceration at 12 hr. It was found that about 2.5 to 3 ml of gastric contents entered the duodenum from 8 to 12 hr

after administration. The reason for the disappearance of these accumulated gastric contents, despite the delayed gastric emptying during this period, remains to be determined. One consideration is that the gastric emptying study involved measurement of the solid contents, yet the accumulated gastric contents primarily consist of liquid. In contrast to in the case of the low doses, the intraduodenal pH remained low, even at 12 hr. This finding indicates that the duodenum could not neutralize the gastric effluent during this period, probably partly due to a reduction in neutralization capacity (22, 23), HCO_3^- secretion (24). At the autopsy at 12 hr, there was a considerably large amount of duodenal contents. Therefore, it is possible that the damaged duodenum could not propel the acidic contents into the lower part of the intestine and so kept the lowered pH.

These findings taken together with the morphologic changes would suggest that the villous damage progressed to ulcers due to this continuous decrease in the intraduodenal pH caused by the delivery of a relatively large amount of accumulated gastric contents into the duodenum.

Duodenal ulcers, in response to mepirizole and cysteamine, usually developed in two opposing parts, "kissing ulcers", of the proximal duodenum (1, 3). To explain the location of damage, Mersereau and Hinchey (25) proposed that gastric juice enters through two channels into the duodenum, so that two ulcers develop. Therefore, we postulated that intraluminal and/or intraabdominal pressure might forcibly push a part of the accumulated gastric contents into the duodenum continuously or intermittently, probably through two channels.

The ulcers induced by mepirizole and cysteamine became severe with time; i.e., most of the ulcers became deep and were frequently perforated after 24 hr (1, 3). It will be worthwhile studying how the initial ulcers, that had developed by 12 hr after administration of the high doses, progressed to severe ones, despite the disappearance of the accumulated gastric contents. Determination of intraduodenal pH from 12 to 24 hr is the subject of an ongoing study in our laboratory.

We conclude that the accumulation of

gastric contents, at least for 8 hr, leading to continuous decrease in the intraduodenal pH for 8 to 12 hr, is a prerequisite for the progression of villous damage to ulceration in response to the two ulcerogens.

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