Impairment of Acid-Neutralizing Capacity and Lesion Formation in the Rat Duodenum during Hemorrhagic Shock: Comparative Study with Indomethacin

Koji TAKEUCHI, Osamu FURUKAWA, Hironori TANAKA, Hideyuki NISHIWAKI and Susumu OKABE
Department of Applied Pharmacology, Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

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Abstract—The effects of hemorrhagic shock (HE) on duodenal pH, acid-neutralizing capacity and mucosal tolerance to acid were investigated in anesthetized rats, and they were compared with those of indomethacin. HE was performed by bleeding from the carotid artery to reduce arterial blood pressure to about 55 mmHg (3 ml of bleeding per 200 g of body weight), and indomethacin was given s.c. in a dose of 5 mg/kg. Duodenal pH was determined in the outflow from the proximal duodenum (1.7 cm) which was perfused with 10^{-4} M HCl, and acid-neutralizing capacity was measured by back-titration of the perfusate to pH 4.0 with 10 mM HCl. Under these conditions, duodenal pH was kept at around 6.0 as the result of neutralization in the loop (~8 μEq/hr). Both HE and indomethacin significantly decreased the pH and acid-neutralizing capacity. Administration of 16,16-dimethyl prostaglandin E_{2} (16-dmPGE_{2}: 30 μg/kg, s.c.) significantly increased both pH and acid-neutralizing capacity in normal and indomethacin-treated rats, but failed to affect these parameters in rats under HE conditions. When the duodenal loop was perfused with 50 mM HCl for 1.5 hr, both HE and indomethacin induced extensive damage in the mucosa. Pretreatment with 16-dmPGE_{2} significantly reduced the formation of duodenal lesions induced by indomethacin but not by HE. These results suggest that HE as well as indomethacin impaired duodenal acid-neutralizing capacity to reduce the tolerance to acid of the mucosa. The deleterious effects of HE on the mucosa may be mainly due to a decreased mucosal blood flow, but not due to a deficiency of endogenous prostaglandins.

Recent studies have shown that alkaline secretion from the surface epithelial cells as well as mucosal blood flow may play an important role in the mechanisms of gastro-duodenal mucosal defense against acid (1–4). However, the relationship between mucosal blood flow and alkaline secretion remains to be defined. The hemorrhagic shock model has been frequently used to investigate the relationship between mucosal blood flow and formation of gastric mucosal injury (3–5). Lillehei et al. (6) showed that hemorrhagic shock potentiated duodenal mucosal lesions induced by histamine injections in dogs. Recently, we reported that histamine induced duodenal lesions in rats when duodenal acid-neutralizing capacity was reduced by concomitant administration of indomethacin (7, 8). Thus, it may be assumed that hemorrhagic shock also affects the acid-neutralizing capacity in the duodenum to reduce the mucosal tolerance to acid.

In the present study, we therefore examined the effects of hemorrhagic shock on duodenal pH, acid-neutralizing capacity and mucosal tolerance to acid in anesthetized rats, and we compared them with those of indomethacin. Since it has been shown that transmucosal potential difference (PD) in the duodenum is associated with the process of alkaline
secretion and the degree of mucosal blood flow (9, 10), changes in duodenal PD were also monitored in various conditions.

Materials and Methods

Male Sprague Dawley rats (200–250 g), kept in individual cages with raised mesh bottoms, were deprived of food but allowed free access to water for 24 hr before the experiments. Each study was carried out using 4 to 6 rats per group.

Operative procedures: The rats were anesthetized with urethane (Nakarai, 1.25 g/kg, i.p.), tracheostomy was performed, and a polyethylene tube was inserted to ensure a patent airway. Another fine polyethylene tube was inserted in the right carotid artery for monitoring blood pressure (BP) and for removal of blood. Temperature was maintained at around 37°C using an external heat lamp (60 watt).

Determination of duodenal pH and PD: Simultaneous measurement of luminal pH and PD in the proximal duodenum was performed according to a previous paper (8). Briefly, the abdomen was opened, and both the stomach and duodenum were exposed. An acute gastric fistula was prepared by means of a polyethylene tube in the fore-stomach through which gastric contents were withdrawn to prevent accumulation of gastric juice in the stomach. A duodenal loop was made between the pyloric ring and the area just proximal to the outlet of the common bile duct (1.7 cm), excluding the influences of bile and pancreatic juice. This loop was perfused at a flow rate of 1.3 ml/min with 10^{-4} M HCl (pH 4.0) made isotonic with NaCl. An exiting tube was connected to a glass electrode of the flow type (Horiba, Model 6901–25T), by which the pH of the duodenal perfusate was continuously measured. The duodenal PD was determined using two agar bridges, one positioned in the duodenal loop and the other in the abdominal cavity. Changes in both pH and PD were continuously monitored on a Hitachi two channel recorder (Model 056).

Determination of acid-neutralizing capacity: Acid-neutralizing capacity was determined by introduction of an automatic titrator (Hiranuma Comitite-7) in the above perfusion system. Amounts of acid neutralized in the loop was measured by back titration of the duodenal perfusate to pH 4.0 using a pH-stat method and by adding 10 mM HCl.

Experimental protocols: [First study] Approximately 30 min after both pH and PD had stabilized, indomethacin (Sigma, 5 mg/kg) or 16,16-dimethyl prostaglandin E_{2} (16-dm-PGE_{2}: Funakoshi, 30 µg/kg) was given s.c. in a volume of 0.5 ml per 100 g of body weight. In another group, the animals were individually bled in an amount of 2 or 3 ml per 200 g of body weight, from the carotid artery, and the BP was simultaneously monitored using a pressure transducer (Narco Tele Care, LTD-5) and a polygraph (San-Ei, 6M-72). These degrees of hemorrhagic shock caused reduction in the BP from 116±11 mmHg to 78±15 mmHg and 56±16 mmHg, respectively. Changes in pH and PD were measured during a test period (3 hr), and the animals were killed by injecting saturated KCl, i.v., at the end of experiments. In some cases, the effect of 16-dmPGE_{2} (30 µg/kg) on duodenal pH and PD was examined in the above perfusion system. Approximately 30 min after acid-neutralizing capacity had stabilized, the animals were given indomethacin or 16-dmPGE_{2}, or subjected to hemorrhagic shock (3 ml of bleeding). 16-dmPGE_{2} was given s.c. 1 hr after indomethacin treatment or the onset of hemorrhagic shock. [Second study] The effects of indomethacin (5 mg/kg), 16-dmPGE_{2} (30 µg/kg) and hemorrhagic shock (2 ml and 3 ml of bleeding) on duodenal acid-neutralizing capacity were examined in the above perfusion system. Approximately 30 min after acid-neutralizing capacity had stabilized, the animals were given indomethacin or 16-dmPGE_{2}, or subjected to hemorrhagic shock, and the titration was continued for 1 hr thereafter. In some cases, 16-dmPGE_{2} was given 30 min after indomethacin treatment or the onset of hemorrhagic shock. [Third study] The effects of indomethacin (5 mg/kg), 16-dmPGE_{2} (30 µg/kg) and hemorrhagic shock (3 ml of bleeding) on duodenal mucosa were examined in the perfusion system by perfusing the duodenal loop with 50 mM HCl. The animals were given indomethacin or bled from the carotid artery, immediately before perfusion of the loop with 50 mM HCl. In some cases, 16-dmPGE_{2} (30 µg/kg) was given 30 min before indomethacin treatment.
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or the onset of hemorrhagic shock. Ninety minutes later, the animals were killed, and the duodenums were removed, inflated by injecting 1 ml of 2% formalin, immersed for 10 min in 2% formalin to fix both the inner and outer layers, and opened along the mesenteric attachment. The area (mm²) of macroscopically visible damage was measured under a dissecting microscope with square grid (x 10) and used as a lesion index. The person measuring the lesion did not know the treatment given to the animals. In every study, indomethacin was suspended in saline with a trace of Tween 80 (Nakarai), and 16-dmPGE₂ was first dissolved in absolute ethanol and diluted with saline immediately before use. Control animals were given the vehicle alone.

Statistics: Data are presented as the mean±S.E. from 4 to 6 rats per group. Values are compared using Dunnett's multiple comparison test (11) for unpaired variates and are considered to be statistically significant if P<0.05.

Results

Effects of indomethacin and hemorrhagic shock on duodenal pH and PD: When the duodenal loop was perfused with 10⁻⁴ M HCl solution (pH 4.0), the pH of the duodenal outflow was 6.0±0.1 and remained in this range during a test period, suggesting a significant neutralization with HCO₃⁻ secretion in the loop (Table 1). Duodenal PD was maintained at values of −1.8 mV to −2.2 mV (mucosa negative) under the above conditions. Administration of indomethacin (5 mg/kg, s.c.) significantly reduced the pH from 6.1±0.1 to 5.4±0.2 with a slight fall in the PD (−1.9±0.07 mV to −1.6±0.08 mV, P<0.05) (Fig. 1). In contrast, both pH and PD were significantly increased by 16-dmPGE₂ (30 µg/kg, s.c.); in this case, the pH rose from 6.1±0.1 to 6.8±0.2 within 30 min. On the other hand, following hemorrhagic shock, duodenal PD decreased immediately, followed by a reduction of the pH (Fig. 2). These changes in pH and PD occurred in association with the degrees of hemorrhagic shock, and the pH was significantly reduced from 6.4±0.2 to 5.2±0.2 in response to 3 ml of bleeding per 200 g of body weight. Administration of 16-dmPGE₂ (30 µg/kg, s.c.) markedly increased the reduced pH caused by indomethacin (5 mg/kg, s.c.), but failed to affect the pH during hemorrhagic shock (Fig. 3).

Effects of indomethacin and hemorrhagic shock on duodenal acid-neutralizing capacity: Under normal conditions, the amount of acid neutralized in the loop was approximately 1–1.5 µEq/10 min (8.3±0.9 µEq/hr). The acid-neutralizing capacity was significantly reduced to 4.0±0.7 µEq/hr by indomethacin (5 mg/kg, s.c.), while 16-dmPGE₂ (30 µg/kg, s.c.) increased the neutralizing capacity

Table 1. Effects of indomethacin, 16,16-dimethyl prostaglandin E₂ and hemorrhagic shock on duodenal pH and PD in anesthetized rats

| Treatment                  | No. of rats | pH Before | PD Before | pH After | PD After |
|---------------------------|-------------|-----------|-----------|----------|----------|
| Saline                    | 4           | 6.1±0.1   | 1.9±0.05  | 6.1±0.1  | 1.9±0.06 |
| Indomethacin (5 mg/kg)    | 5           | 6.1±0.1   | 1.9±0.07  | 5.4±0.2* | 1.6±0.08*|
| 16,16-dmPGE₂ (30 µg/kg)   | 5           | 6.1±0.1   | 1.8±0.05  | 6.8±0.2* | 2.3±0.10*|
| Saline                    | 4           | 6.4±0.2   | 2.0±0.05  | 6.1±0.2  | 2.0±0.06 |
| Hemorrhagic shock (2 ml)  | 5           | 6.3±0.2   | 2.1±0.09  | 5.6±0.3  | 1.6±0.10*|
| Hemorrhagic shock (3 ml)  | 5           | 6.4±0.2   | 2.1±0.10  | 5.2±0.2* | 1.1±0.06*|

All values are presented as the mean±S.E. from 4 to 5 rats per group. The proximal duodenum was perfused with acid (pH 4.0) during a test period. Indomethacin and 16,16-dmPGE₂ were given subcutaneously, and hemorrhagic shock was caused by bleeding from the carotid artery in an amount of 2 or 3 ml of blood per 200 g body wt. Values in the columns indicated as Before and After are those observed immediately before and 30 min after treatments, respectively. *Statistically significant difference from the saline controls, at P<0.05.
Fig. 1. Representative figures showing the effects of indomethacin (5 mg/kg) and 16,16-dimethyl prostaglandin E2 (30 µg/kg) on duodenal pH and PD in anesthetized rats. The duodenal loop was perfused with 10^{-4} M HCl solution, and indomethacin or 16,16-dimethyl prostaglandin E2 was given subcutaneously. The animals were killed by injecting saturated KCl intravenously at the end of the experiments.

Fig. 2. Representative figures showing the effects of hemorrhagic shock on duodenal pH and PD in anesthetized rats. Hemorrhagic shock was caused by bleeding 2 or 3 ml from the carotid artery. The animals were killed by injecting saturated KCl intravenously at the end of the experiments.

Effects of indomethacin and hemorrhagic shock on mucosal tolerance to acid: Perfusion of the duodenal loop for 90 min with 50 mM HCl did not induce macroscopic damage in the mucosa (not shown). Neither indomethacin (5 mg/kg, s.c.) nor hemorrhagic shock (3 ml of bleeding) alone had any effect on the duodenal mucosa (not shown). However, perfusion of the mucosa with 50 mM HCl produced gross damage in widespread areas within 90 min under indomethacin treatment or following hemorrhagic shock, the lesion index being 135.3±9.0 mm² or 116.7±9.4 mm², respectively (Table 2). Pretreatment with 16-dmPGE₂ (30 µg/kg, s.c.) significantly reduced the formation of duodenal lesions induced by 50 mM HCl perfusion plus indomethacin (43.6%), but
Fig. 3. Representative figures showing the effects of 16,16-dimethyl prostaglandin E₂ (30 μg/kg, s.c.) on duodenal pH and PD in anesthetized rats treated with indomethacin (5 mg/kg, s.c.) or subjected to hemorrhagic shock (3 ml of bleeding). The duodenal loop was perfused with 10⁻⁴ M HCl solution, and the animals were killed by injecting saturated KCl intravenously at the end of the experiments.

Fig. 4. Effects of 16,16-dimethyl prostaglandin E₂ (30 μg/kg), indomethacin (5 mg/kg) and hemorrhagic shock (2 ml and 3 ml of bleeding) on acid-neutralizing capacity of the duodenum in anesthetized rats. 16,16-Dimethyl prostaglandin E₂ and indomethacin were given subcutaneously, and hemorrhagic shock was caused by bleeding from the carotid artery. In the combined treatment, 16,16-dimethyl prostaglandin E₂ was given 30 min after indomethacin treatment or the onset of hemorrhagic shock. Values of acid-neutralizing capacity represent the total amount of acid neutralized for 1 hr after administration of each agent or the onset of hemorrhagic shock, and they are presented as the mean±one S.E. from 6 rats. *Statistically significant difference from the control, at P<0.05.
Table 2. Effects of 16,16-dimethyl prostaglandin E2 on duodenal mucosal injury induced by 50 mM HCl perfusion plus indomethacin treatment or hemorrhagic shock in anesthetized rats

| Conditions                | Treatment | Dose (μg/kg) | No. of rats | Lesion index (mm²) | Inhibition (%) |
|---------------------------|-----------|--------------|-------------|--------------------|---------------|
| Indomethacin plus 50 mM HCl | Saline    | —            | 6           | 135.3± 9.0         | —             |
|                           | 16-dmPGE₂ | 30           | 6           | 76.3± 10.0*        | 43.6          |
| Hemorrhagic shock plus 50 mM HCl | Saline    | —            | 7           | 116.7± 9.4         | —             |
|                           | 16-dmPGE₂ | 30           | 6           | 115.0± 15.0        | 1.5           |

All values are presented as the mean±S.E. from 6 to 7 rats per group. Indomethacin was given subcutaneously in a dose of 5 mg/kg, and hemorrhagic shock was caused by bleeding from the carotid artery in an amount of 3 ml of blood per 200 g of body weight. 16-dmPGE₂ was given subcutaneously 30 min before indomethacin treatment or the onset of hemorrhagic shock. The duodenum was perfused with 50 mM HCl for 1.5 hr and then examined under a dissecting microscope (×10). *Statistically significant difference from the corresponding control group, at P<0.05.

did not protect the mucosa against injury caused by 50 mM HCl perfusion during hemorrhagic shock (1.5%).

Discussion

Since the proximal part of the duodenum is continuously exposed to acid emptied from the stomach, the duodenum itself should dispose of a greater amount of acid. Passive diffusion of H⁺ ions from the lumen, diffusion or ultrafiltration of tissue HCO₃⁻ into the lumen, secretion by Brunner's glands or a combination of these were proposed as mechanisms responsible for the disappearance of acid (12, 13). However, recent studies showed that this ability may largely be due to neutralization with HCO₃⁻ originating from the surface epithelial cells by an active process (1, 2, 8).

In the present study, the luminal pH and acid-neutralizing capacity were measured in the duodenum perfused with slightly acidic solution (pH 4.0). We previously reported using the same perfusion system that changes in luminal pH are closely associated with those of HCO₃⁻ secretion in the duodenum (8). Therefore, a significant decrease in the acid-neutralizing capacity during hemorrhagic shock may be due to an impairment of HCO₃⁻ secretion in the duodenum. As expected from other studies (7, 8, 14), indomethacin also impaired the acid-neutralizing capacity in the duodenum. Since adaptive increase of HCO₃⁻ secretion is known to be mediated by endogenous prostaglandins (PGs), the above effect of this agent may appear through a deficiency of PGs due to cyclooxygenase inhibition (15). In fact, the deleterious effects of indomethacin on duodenal pH and acid-neutralizing capacity were completely reverted by an exogenous PG (16-dmPGE₂). On the contrary, 16-dmPGE₂ failed to exert apparent effects on both pH and acid-neutralizing capacity during hemorrhagic shock. These results suggest that the mechanisms involved in impairment of duodenal acid-neutralizing capacity may differ between these two conditions.

Leung et al. (16) demonstrated in rats that there is a strong correlation between a reduction in mucosal blood flow and a decrease in arterial BP during hemorrhagic shock. Since in the present study the arterial BP was reduced to about 55 mmHg after hemorrhagic shock (3 ml of bleeding), it may be assumed that mucosal blood flow is sufficiently decreased during hemorrhagic shock. Simson et al. (9) showed using an in vitro preparation of amphibian duodenum that HCO₃⁻ secretion was markedly reduced by removal of HCO₃⁻ from the nutrient solution. Schiessel et al. (17) reported a significant decrease of duodenal HCO₃⁻ secretion after hemorrhagic shock in rabbits. Since hemorrhagic shock reduced mucosal blood flow by decreasing blood volume due to bleeding, this treatment might reduce the availability of HCO₃⁻ in the blood, just like...
what was observed in the above in vitro experiment (9). On the other hand, a recent study showed that hypoxic conditions induced by a constriction of blood vessels or anoxia enhances the formation of PGs in the endothelial cells (18). If the same event occurs in response to hemorrhagic shock, a deficiency of PGs may be excluded in the mechanisms of impaired acid-neutralizing capacity during hemorrhagic shock. This may be a reason why 16-dmPGE_2 had less effect on duodenal pH and acid-neutralizing capacity in rats subjected to hemorrhagic shock.

The cause-effect relationship between the acid-neutralizing capacity and duodenal lesions has been suggested by several experimental ulcer models (7, 19–21). Gallagher and Szabo (19) and Tanaka et al. (20) showed a marked increase of acid load in the duodenum following administration of cysteamine and mepirizole in rats, and they suggested that the increased amount of acid in the duodenum may be directly associated with formation of duodenal lesions. Water-immersion stress also impaired acid-neutralizing capacity and produced damage in the rat duodenum when acid hypersecretion was concomitantly present (21). Both hemorrhagic shock and indomethacin induced extensive damage in the duodenum perfused with 50 mM HCl. These results support the above findings that the impaired acid-neutralizing capacity may play an important role in the etiology of duodenal lesions. The severity of duodenal damage induced by indomethacin was slightly greater as compared to that produced during hemorrhagic shock, despite similar degrees of reduction in the acid-neutralizing capacity being observed under these two conditions. Since indomethacin causes a deficiency of PGs (15) and since PGs affect a variety of functions in the gastrointestinal tract (22), it may be possible to assume that indomethacin has deleterious influences on other defensive mechanisms besides acid-neutralizing capacity in the duodenum. The different responses of 16-dmPGE_2 on duodenal lesions induced by indomethacin and hemorrhagic shock would be understandable based on the effects of this agent on duodenal pH and acid-neutralizing capacity under these conditions.

In the present study we also noted that duodenal PD altered in association with luminal pH (acid-neutralizing capacity). Since acid-neutralizing capacity reflects HCO_3^- secretion from the surface epithelial cells (8), these results seem to be consistent with the findings by others that duodenal HCO_3^- secretion is an electrogenic process and is accompanied by a rise in duodenal PD (1, 9, 23). Although PD is a net expression of many contributing factors (10), and we cannot interpret PD alterations based on HCO_3^- secretion only, a simultaneous measurement of PD and pH (HCO_3^- secretion) may be useful for understanding the mechanisms of duodenal alkaline secretion.

Taken together, the present study suggests that hemorrhagic shock as well as indomethacin reduced the mucosal tolerance to acid of the duodenum by impairing acid-neutralizing capacity. The latter effect may result from a deficiency of mucosal PGs, while the effect of hemorrhagic shock may be due mainly to decrease of mucosal blood flow caused by a reduced blood volume and may be independent from a PG deficiency. Since adequate mucosal blood flow contributes to the mucosal defense by removal of acid back-diffused into the mucosa, hemorrhagic shock may have deleterious effects on both intraluminal and intramucosal neutralization of acid, and thereby increases the susceptibility of the mucosa to acid.

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