Protective Effect of Cisapride against Indomethacin-Induced Obstruction of the Gastric Mucosal Hemodynamics in Rats

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ABSTRACT—We investigated the effect of cisapride, a gastroprokinetic agent, on the obstructed gastric mucosal hemodynamics induced by indomethacin using an organ reflectance spectrophotometry system in rats. Indomethacin (10 mg/kg, i.v.) reduced both the gastric mucosal blood volume and the gastric mucosal blood oxygenation. Pretreatment with cisapride (0.1 mg/kg, i.v.) prevented these deteriorations. The presently-clarified gastric mucosal protective effect of cisapride may contribute to its therapeutic efficacy.

Keywords: Cisapride, Stomach, Mucosal blood flow

Cisapride is a gastroprokinetic drug that releases acetylcholine by acting on the 5-hydroxytryptamine$_4$ receptor subtype (1). It is well documented that cisapride stimulates the gastrointestinal motor function in humans as well as animals (2, 3). Clinically, cisapride is effective for the treatment of gastrointestinal disorders, including gastroesophagal reflex, gastroparesis, nonulcer dyspepsia, small bowel dysmotility, idiopathic intestinal pseudo-obstruction and constipation (2).

The gastric mucosal blood flow plays an important role in the pathogenesis and healing of mucosal lesions (4-6). Cisapride increases the basal mucosal blood flow in the canine gastric antrum (7). However, the effect on the obstructed mucosal microcirculation has not been studied. In the present study, we investigated the effect of cisapride on the indomethacin-induced obstruction of gastric mucosal blood volume and tissue oxygenation in anesthetized rats. Preliminary results of this work have been presented at a Meeting during the First United European Gastroenterology Week, Athens (8).

Male Sprague-Dawley rats weighing 200-300 g, fasted for 24 hr, were anesthetized by urethane (1.25 g/kg, i.p.), and their body temperature was maintained at 37±1℃ with a temperature controller (CMA/150; Carnegie Medicine, Stockholm, Sweden). The gastric mucosal hemodynamics was measured according to the method of Sato et al. (4). In brief, after a midline incision, the stomach was exposed, and a part of the greater curvature of the forestomach was incised. Thereafter, a light-conducting optic fiber probe of the organ reflectance spectrophotometry system (TS-200; Sumitomo Electric Industries, Osaka) was introduced to the corpus of the stomach and was gently placed on the mucosa of the corpus. The refrectance spectrum of the mucosa was obtained through the probe every 10 min. The indexes of the hemoglobin concentration (IHb) and the degree of the hemoglobin oxygenation (ISO_2) in the mucosal capillary were calculated from the spectrum. IHb has been shown to have a good correlation with the mucosal blood flow measured by the hydrogen clearance method (6), and ISO_2 has been shown to correlate well with the tissue oxygen tension measured by a needle type oxygen electrode (9). After a stabilization period of more than 15 min, cisapride (0.1 mg/kg; Janssen-Kyowa Co., Ltd., Tokyo) or the vehicle was intravenously administered to the animal. At 30 min later, 10 mg/kg of indomethacin (Sigma Chemical Co., Ltd., St. Louis, MO, USA), dissolved in 5% $NaHCO_3$, was administered. Each drug was administered into the cannula placed in the femoral vein. IHb and ISO_2 were expressed as the percentage of the value at the time of the administration of indomethacin. All data were expressed as means±S.E. The Aspin-Welch test was carried out to determine significant differences between the vehicle- and cisapride-treated group. P-values of less than 0.05 were

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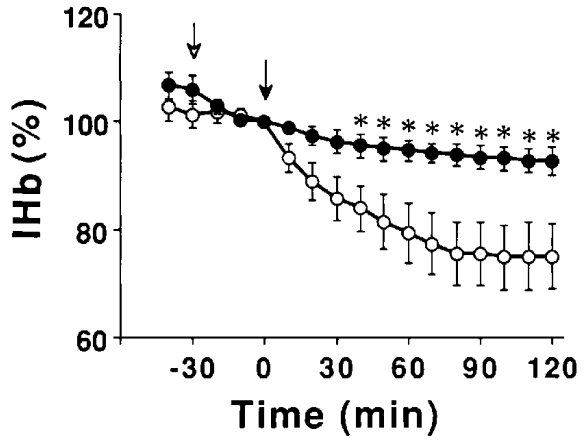

Fig. 1. Effect of cisapride on the reduction of gastric mucosal blood volume (IHb) induced by indomethacin in rats. Open arrow: 0.1 mg/kg of intravenous cisapride (closed circle, n=4) or the vehicle (open circle, n=7). Closed arrow: 10 mg/kg of intravenous indomethacin. Values are expressed as means±S.E. *P<0.05, compared with the value of the vehicle-treated group at the corresponding time point (Aspin-Welch test).

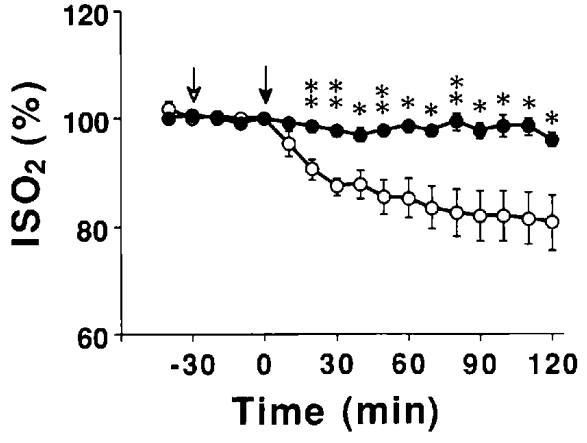

Fig. 2. Effect of cisapride on the reduction of gastric mucosal blood oxygenation (ISO_2) induced by indomethacin in rats. Open arrow: 0.1 mg/kg of intravenous cisapride (closed circle, n=4) or vehicle (open circle, n=7). Closed arrow: 10 mg/kg of intravenous indomethacin. Values are expressed as means±S.E. *P<0.05, **P<0.01, compared with the value of the vehicle-treated group at the corresponding time point (Aspin-Welch test).

considered to be statistically significant.

The administration of indomethacin gradually decreased IHb, indicating a decrease in the gastric mucosal blood flow. The value of IHb at 90 min after the administration was 76±5.8% (n=7). Pretreatment with cisapride significantly (P<0.05) prevented this decrease at 40 to 120 min following the administration of indomethacin (Fig. 1). IHb in the cisapride-treated group was 94±2.2% (n=4) at 90 min after the administration of indomethacin. In regard to the mucosal tissue oxygenation, indomethacin also decreased ISO_2 to the level of 82±4.7% (n=7) at 90 min (Fig. 2). This reduction suggests that the mucosa was in the state of hypoxia. Pretreatment with cisapride significantly (P<0.05) improved this decrease at 20 min and thereafter. The rate at 90 min was 98±1.4% (n=4) (Fig. 2).

In the present study, the administration of indomethacin obscured the gastric mucosal hemodynamics, as examined by the determination of the change of both the mucosal hemoglobin concentration and hemoglobin oxygenation. It is known that indomethacin reduces the gastric mucosal blood flow (10), although the mechanism involved in this reduction has not been fully clarified. Prostaglandins are thought to protect the mucosa by increasing mucosal blood flow, secreting mucus and bicarbonate, and inhibiting of neutrophil function (11-14). Therefore, it is likely that indomethacin, a cyclooxygenase inhibitor, reduced gastric mucosal blood volume by inhibiting prostaglandin synthesis. However, Arakawa et al. reported that exogenous administration of 16,16-dimethyl prostaglandin E_2 did not alter the indomethacin-induced reduction of gastric mucosal blood flow in rats (15). Thus, more detailed study is required to elucidate precisely how indomethacin reduces the gastric mucosal blood flow. Nonetheless, the obstruction of gastric mucosal hemodynamics by indomethacin probably plays an important role in the indomethacin-induced gastric ulceration.

Osuga et al. reported that cisapride enhanced the mucosal blood flow in the antrum but not in the corpus in normal anesthetized dogs (7). They supposed that cisapride increases the mucosal blood flow in the antrum through the release of acetylcholine, because atropine abolished the increase in the blood flow. In the present study using the corpus of rats, the administration of cisapride alone did not significantly change the mucosal hemodynamics. The mucosal blood flow in the corpus is relatively abundant as compared with that in the antrum (4, 7). A high level of basal blood volume might be the reason why cisapride did not enhance IHb in the corpus. In contrast, when IHb and ISO_2 were reduced by indomethacin, cisapride reversed the reduction. This result suggests that in the corpus, cisapride does not affect the basal mucosal blood flow, but this drug prevents the obstruction of the blood flow.

The main action of cisapride is to enhance the gastrointestinal motility (2, 3), resulting in the improvement of the digestive symptoms. The present study demonstrated, for the first time, that cisapride ameliorates the obstruction of gastric mucosal hemodynamics. The protective effect against the obstruction of gastric hemodynamics may also contribute to the clinical efficacy of cisapride.

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