Impaired Neutralizing Capacity of Duodenal Mucosa Following Luminal Acidification in Recurrent Duodenal Ulcer

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To investigate the role of the mucus-bicarbonate barrier in the prevention of duodenal ulcer recurrence, duodenal mucosal neutralizing capacity and mucosal prostaglandin (PG) synthesis were examined in 5 normal controls (NC) and 12 duodenal ulcer (DU) patients. DU patients were divided into non-recurrent (NR, 7) and recurrent (R, 5) groups based on endoscopic follow-up study. The recovery time (RT) was significantly longer and the mucosal PGE₂ synthesis was significantly lower in R than in NC and NR groups. There was a proportional correlation between mucosal PG synthesis and RT in DU patients. These results indicate that impaired neutralizing capacity caused by reduced endogenous PG synthesis in duodenal mucosa may contribute to recurrence of DU.

Key words: Prostaglandin, Neutralizing capacity, Ulcer recurrence

It has been reported that the neutralizing capacity of duodenal mucosa (1) and mucosal prostaglandin (PG) synthesis (2) are impaired in duodenal ulcer (DU). However, little is known about the mechanisms involved in the recurrence of DU. It can be hypothesized that the impaired neutralizing capacity brought about by reduced endogenous PG synthesis in the duodenal mucosa may contribute to DU recurrence. The purpose of the present study was to verify this hypothesis by comparison of the duodenal mucosal neutralizing capacity and the mucosal PG synthesis between normal control (NC), non-recurrent (NR) and recurrent (R) groups.

PATIENTS AND METHODS

Patients and controls

The present study was carried out on 5 NC and 12 DU patients who were endoscopically diagnosed to have active duodenal ulcers in the duodenal bulb at the University Hospital of Tsukuba. None of the patients received strong antisecretory drugs such as anticholinergics, histamine H₂ receptor antagonists for at least 1 yr before starting the present study. After the active ulcer was found, all patients were treated with antacid (3 g/day) during the follow-up period unless they had severe symptoms. Cimetidine (400 mg/day) was temporarily used only for relief from the symptoms. None of the patients had complicating diseases, and none took other drugs during the follow-up period. Ulcer healing was confirmed by endoscopy based on the disappearance of the white coat on the ulcer. After confirming that each case of DU had healed, duodenal mucosal neutralizing capacity and mucosal PG synthesis were examined. In order to monitor recurrence, patients were followed for 1 yr by periodical endoscopic examination performed at three-month intervals. DU patients were divided into NR and R groups based on endoscopic follow-up study.

NR group included 7 patients (mean age 44.3 yr,
range 33–51) who did not experience recurrence for 1 yr. R group included 5 patients (mean age 47.4 yr, range 46–51) who had a recurrence within 1 yr. All the subjects in the NC group (mean age 37.4 yr, range 28–40) were endoscopically confirmed to have no lesions in the upper gastrointestinal tracts. Each subject gave written informed consent, and the study was approved by the Human Subjects Committee at our institution.

Mucosal neutralizing capacity

Measurement of juxtamucosal pH was carried out using a flexible pH electrode (Kobayashi Medical Model) with a 1.3 mm tip diameter and a 1 mm pH sensitive tip. For the infusion of 0.1 N HCl, a polyvinyl tube was attached to the upper gastrointestinal endoscope (Olympus XQ 10) (Fig. 1). Before introduction of the endoscope, the throat was sprayed with 1% lidocaine and sedation was induced with intramuscular diazepam. After the endoscope was inserted into the duodenal bulb, the electrode was passed through the biopsy channel and the electrode tip was gently advanced under direct vision until it touched the mucosa where the juxtamucosal pH reading was obtained. The tip was placed at the visually normal mucosa of the duodenal cap. After obtaining stable pH values, 10 ml of 0.1 N HCl was infused through the tube for 1 min, and the changes in the juxtamucosal pH of the duodenal cap were continuously recorded. The basal juxtamucosal pH (basal pH) and the recovery time needed for the juxtamucosal pH to return to its pre-infusion value (RT), which were considered to be an index of mucosal neutralizing capacity, were measured. To evaluate the reflux of pancreatic juice, the residual fluid on the duodenal cap was collected and the levels of amylase were measured by the method of Somogyi.

Mucosal PGE2 synthesis

One week after the study, two mucosal specimens (mean weight 15–20 mg) were endoscopically obtained from the normal mucosa of the duodenal cap. Mucosal PGE2 synthesis was determined by measurement of the PGE2 released into the medium during a 2-h incubation period, according to the method of Sharon et al (3). PGE2 was determined by radioimmunoassay (Amersham PGE2 kit).

Data analysis

Results are expressed as mean ± SE. Student’s t-test for the analysis of unpaired values and correlation coefficients was used. Differences were considered significant at p < 0.05.

RESULTS

Mucosal neutralizing capacity

Stable juxtamucosal pH recordings were obtained in all subjects. Figure 2 illustrates the complete data from a subject of the NR group (patient 1), and Fig.

![Fig. 1. Close-up view of the distal end of the electrode and endoscope.](image)

![Fig. 2. Recording of juxtamucosal pH measurements in a subject in the NR group.](image)
Neutralizing Capacity of Duodenal Mucosa

Fig. 3. Recording of juxtamucosal pH measurements made in a subject in the R group.

Fig. 4. Recovery time (RT) obtained from NC, NR and R groups. Individual values and mean ± SE. *p < 0.05

Fig. 5. Basal juxtamucosal (basal pH) obtained from NC, NR and R groups. Individual values and mean ± SE.

Fig. 6. PGE$_2$ accumulation in the medium during the 120-min culture of duodenal biopsy specimens obtained from NC, NR, R and DU (NR + R) groups. Individual values and mean ± SE. *p < 0.05

3 from an R group patient (patient 2). After infusion of acid, the value of juxtamucosal pH fell and gradually returned to the previous value. A remarkable difference in RT (---) was demonstrated between patient 1 and patient 2. Regarding the basal pH, no difference was found between patient 1 and patient 2. RT was significantly longer in the R group (6.5 ± 0.3 min) than in the NC
Mucosal PGE2 synthesis

Figure 6 shows that the duodenal mucosal PGE2 synthesis was significantly lower in the R group (19 ± 3 pg/mg prot/h) than in the NC (36 ± 4) and NR (34 ± 3) groups and that there was no difference in duodenal mucosal PGE2 synthesis between the NC and DU (NR ± R) groups (28 ± 4).

Correlation between mucosal PGE2 synthesis and RT

There was a linear correlation between mucosal PGE2 synthesis and RT in the DU group (Fig. 7).

DISCUSSION

It has been reported that a pH gradient exists across the duodenal mucus layer, with the pH at the epithelial surface maintained near neutrality while luminal pH is acidic (4). Furthermore, Quigley and Turnberg measured the juxtamucosal pH and detected a pH gradient in the human duodenal cap using microelectrodes endoscopically (5). Their results indicated that the mucus-bicarbonate barrier inhibits mucosal acidification in humans and that the duodenal mucosa in DU patients is less capable of maintaining an adjacent neutral zone in the face of luminal acid. In the present study, the change in juxtamucosal pH following luminal acidification was measured endoscopically and the RT was calculated. Regarding the definition of an index of the mucus-bicarbonate barrier, it has been reported that in the duodenum of dogs and humans when the luminal pH is as low as 2.0 the juxtamucosal pH is neutral and that the juxtamucosal pH begins to fall in the face of a luminal pH of <1.5 (6). In this study, with a luminal pH as low as 1.0 for 1 min, the juxtamucosal pH fell momentarily and the time required for the juxtamucosal pH value to return to its pre-infusion value was measured. Therefore, RT was dependent upon duodenal bicarbonate secretion and the duodenal mucus gel structure after luminal acidification and was indicative of the duodenal mucosal neutralizing capacity against an acid load.

The mechanisms involved in duodenal mucosal bicarbonate production and duodenal mucus gel structure are multifactorial. Several gastrointestinal hormones (VIP, secretin, etc.) and neuropeptides stimulate duodenal mucosal bicarbonate secretion in animals. Among the most potent agonists of duodenal mucosal bicarbonate secretion are PG of the E class. It has been previously reported that intraduodenal acid infusion induces mucosal PG generation (7) and that PG stimulates duodenal mucosal bicarbonate secretion (8) and thickens the mucus layer (9). In the present study, the RT was significantly longer and duodenal mucosal PGE2 synthesis was significantly lower in the R than in the NR group. Furthermore, there was a proportional correlation between RT and duodenal mucosal PGE2 synthesis in DU patients. These results indicate that the impaired neutralizing capacity caused by reduced endogenous PG synthesis in the duodenal mucosa may be a factor in the recurrence of DU.

Recent studies, however, have shown the existence of another type of acid disposal mechanism termed the paracellular pathway, which is independent of PG (10). To confirm the role of PG, it is necessary to clarify whether or not the ad-
ministration of exogenous PG shortens the RT in the R group.

Previous studies on the basal mucosal PG synthesis have shown a large overlap between DU patients and normal subjects (11, 12).

In the present study, however, at the basal state (without acid load), duodenal mucosal PGE$_2$ synthesis was lower in the R than in the NR group. Therefore, we propose that basal mucosal PG synthesis is impaired in the R group and that this abnormality might be characteristic of DU patients who tend to frequently have recurrence. Whether these abnormalities are the cause or result of recurrence can’t be deduced from this study.

Concerning the pathogenesis of DU recurrence, few papers have been published. We previously reported that increased parietal cell responsiveness contributes to the recurrence of DU (13). We proposed that abnormalities in both mucosal defense and luminal attack may together contribute to the recurrence of DU.

It should be emphasized, however, that the number of patients and control subjects in this study was small. Thus the present results must be confirmed using a variety of technical approaches and broader groups of individuals.

REFERENCES


