Prevention of Indomethacin-Induced Gastric Mucosal Injury in \textit{Helicobacter pylori}-Negative Healthy Volunteers: A Comparison Study Rebamipide vs Famotidine

Yuji Naito$^{1,2,3,*}$, Shoji Iinuma$^{2,3}$, Nobuaki Yagi$^{2}$, Yoshio Boku$^{2,3}$, Eiko Imamoto$^{3}$, Tomohisa Takagi$^{2}$, Osamu Handa$^{2}$, Satoshi Kokura$^{2}$, and Toshikazu Yoshikawa$^{1,2}$

$^1$Medical Proteomics, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan
$^2$Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan
$^3$Department of Medicine, Hikone Central Hospital, Hikone 522-0054, Japan

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\textbf{Summary} The clinical efficacy of gastroprotective drugs or low-dose \textit{H$_2$} receptor antagonists in the prevention of nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy is limited. The aim of the present study was to investigate efficacy of rebamipide and famotidine in \textit{Helicobacter pylori} (\textit{H. pylori})-negative healthy volunteers taking NSAID. This study was a randomized, two way crossover study comparing the preventive effect rebamipide 100 mg, t.i.d. and famotidine 10 mg, b.i.d against indomethacin (25 mg, t.i.d.)-induced gastric mucosal injury in \textit{H. pylori}-negative healthy volunteers. 12 subjects satisfied criteria and were randomized. Endoscopy was performed at baseline and again after the treatment for 7 days, and symptoms were recorded during the treatment. Tissue levels of lipid peroxides and myeloperoxidase and serum indomethacin concentrations were also measured. Subjective symptoms were developed in 58\% (7/12) of the rebamipide group, and in 75\% (9/12) of the famotidine group (no significant differences). The incidence of gastric lesions (modified Lanza score 2 or higher) was 17\% (2/12) in the rebamipide group and 25\% (3/12) in the famotidine group. Peptic ulcers did not occur in both groups. There were no significant differences in tissue levels of lipid peroxide and myeloperoxidase and serum level of indomethacin between two groups after the treatment. In conclusion, these data recommend rebamipide (100 mg, t.i.d.) or famotidine (10 mg, b.i.d.) for the prevention of acute gastric injury induced by NSAID in patients without a particular risk factor.

\textbf{Key Words:} famotidine, gastric injury, indomethacin, rebamipide

\textbf{Introduction}

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin are capable of producing injury to gastrointestinal mucosa in experimental animals and humans, and their use is associated with a significant risk of hemorrhage, erosions, and perforation of both gastric and intestinal ulcers [1]. The molecular basis for the gastrointestinal toxicity of NSAIDs is widely believed to their inhibitory activity against cyclooxygenase, which causes them to block the production of prostaglandins and their therapeutic actions. Suppression of prostaglandin synthesis is associated with reduction of gastric mucosal blood flow, disturbance of microcirculation, decrease in mucus secretion, lipid peroxidation, and neutrophil activation, which are involved in the pathogenesis of gastrointestinal mucosal disorders [1–4]. While the presence of acid in the lumen of the stomach may not be a primary
factor in the pathogenesis of NSAID-induced gastropathy, it can make an important contribution to the severity of these lesions by impairing the restitution process, interfering with hemostasis and inactivating several growth factors that are important in mucosal defense and repair.

To make a strategy for the prevention of NSAID-induced gastropathy, it is important to evaluate the risk factor of each patient. Multiple factors have been identified that increase risk for NSAID-related upper gastrointestinal complications. The highest risks are related to age (65 years) and prior history of peptic ulcer; additional risk factors include use of multiple NSAIDs, high doses of NSAIDs, and use of anticoagulants or steroid. Recent studies suggest that NSAID-induced ulcers in at-risk patients can be prevented largely through co-administration of a proton pump inhibitor to block acid secretion in the stomach \[5, 6\].

The two most common causes of peptic ulcers are use of NSAIDs and infection of *Helicobacter pylori* (*H. pylori*). Although a synergy between *H. pylori* and NSAID use for the development of peptic ulcers and ulcer bleeding has been shown by a meta-analysis, the role played by *H. pylori* in the development of overall gastrointestinal complications remains a subject of controversy [7]. Interestingly, Kamada *et al.* [8] have demonstrated that NSAID-associated gastric ulcer frequently occur in the antrum with bleeding in contrast to non-NSAID-associated gastric ulcers, and that the rate of *H. pylori* infection in NSAID-associated gastric ulcers is significantly lower than that in non-NSAID-associated gastric ulcers. We have also reported that gastric ulcer occurs in 30% of *H. pylori*-negative healthy volunteers taking indomethacin (25 mg, t.i.d., 7 days), and that gastro-protective drug rebamipide markedly inhibited these lesions [9]. The aim of the present was to compare the efficacy and tolerability of rebamipide and normal dose, not high dose, famotidine in the prevention of NSAID-associated gastrointestinal damage and related symptoms in *H. pylori*-negative healthy volunteers.

**Methods**

**Ethics**

This study was conducted by gastroenterologists at the Hikone Central Hospital. The ethics committee at the Hikone Central Hospital approved the study protocol prior to the start of the study, which was conducted in accordance with Good Clinical Practice protocol. Prior to starting this study, the investigators explained in detail to each subject the aim and content of the study and the expected risks and adverse reactions. Prior to participating in the trial, written informed consent was provided by each subject.

**Protocol**

This was a randomized, double blind, two-way crossover study comparing the preventive effect of rebamipide and famotidine against indomethacin-induced gastric mucosal injury in healthy volunteers. All subjects were required to undergo a complete medical history and physical examination, clinical laboratory tests including serum IgG antibody against *H. pylori*, and a normal upper gastrointestinal endoscopy (i.e. grade 0 on the modified Lanza score) before the first dose of each study medications. Subjects were excluded from the study if they had an abnormal baseline endoscopy, history of peptic ulcer disease or gastrointestinal bleeding, a history of chronic disease, or a history of known alcohol abuse or drug dependency. Subjects were also excluded if clinical laboratory tests showed any abnormality or *H. pylori*-positive, or if they received any anti-inflammatory drug within 1 week of the study entry, or any drug within 1 month.

A total of 12 healthy male subjects between the ages of

| No. | Age | Sex | Anti-Hp Ab | Chronic Inflammation | Atrophy |
|-----|-----|-----|------------|----------------------|---------|
|     |     |     |            | antrum | body |      |
| 1   | 20  | male | negative  | 0   | 0 | 0 |
| 2   | 21  | male | negative  | 0   | 0 | 0 |
| 3   | 20  | male | negative  | 0   | 0 | 0 |
| 4   | 22  | male | negative  | 0   | 0 | 0 |
| 5   | 23  | male | negative  | 1   | 0 | 0 |
| 6   | 22  | male | negative  | 0   | 0 | 0 |
| 7   | 23  | male | negative  | 0   | 0 | 0 |
| 8   | 24  | male | negative  | 0   | 0 | 0 |
| 9   | 22  | male | negative  | 0   | 0 | 0 |
| 10  | 24  | male | negative  | 0   | 0 | 0 |
| 11  | 21  | male | negative  | 1   | 1 | 0 |
| 12  | 21  | male | negative  | 0   | 0 | 0 |
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20–24 year who satisfied these inclusion and exclusion criteria received first baseline endoscopic examination, and biopsy specimens were taken from the greater curvature of gastric body and the antrum 4 weeks prior to the therapeutic trial, for the histological evaluation and the measurement of myeloperoxidase (MPO) content and thiobarbituric acid (TBA)-reactive substances. As shown in Table 1, all subjects were male young healthy volunteers with non-atrophic non-inflammatory normal gastric mucosa without \textit{H. pylori} infection. A second endoscopy was performed 4 weeks after the first to confirm disappearance of gastric lesions produced by the first biopsy procedure. Subjects were randomly assigned to one of two-treatment sequence in a two-way crossover design. Each sequence involved indomethacin 25 mg t.i.d. plus rebamipide (Mucosta®; Otsuka Pharmaceutical Co., Inc., Tokyo, Japan) 100 mg t.i.d. and indomethacin 25 mg t.i.d. plus famotidine (Gaster®; Astellas Pharma Inc., Tokyo, Japan) 10 mg b.i.d.. On the first day of treatment, a second endoscopy was performed in the morning and two doses of study medication were then taken over the remainder of the day. On the following 6 days, medication was taken three times daily. Finally, in the morning on day 8, subjects received third endoscopic examination, and biopsy specimens were taken from the greater curvature or circumference of erosion of gastric body and the antrum for the measurement of biochemical parameters. Consecutive study periods were separated by a washout interval of 4 week. A 4th endoscopy was performed 4 weeks after the third to confirm disappearance of gastric lesions.

**Symptoms**

Symptoms were recorded daily during the treatment period; each subject noted the extent and severity of his symptoms.

**Gastric mucosal injury**

The extent of gastric mucosal injury was assessed according to the modified Lanza score (MLS, Table 1) [9, 10]. Endoscopy photographs with 20 or more image cuts were sent to the endoscopic findings judge, who was outside the Hikone central hospital. Endoscopists and the finding judge were not informed of either the study drug or the date of the photographs. To minimize the variance of endoscopy, the same endoscopist used the same type of endoscope to photograph the same region at the same angle for each patient.

**Histological study of gastric mucosa**

Hematoxylin-eosin (H&E)-stained gastric mucosal specimens were used to evaluate the extent of inflammation and atrophy. The gastritis was graded using the visual analog scale of the Updated Sydney System [11] as none (0), mild (1), moderate (2), or marked (3). The following items were evaluated separately: the acute inflammatory component of gastritis (especially the amount of neutrophil infiltration), chronic inflammatory gastritis (lymphoplasmacytic infiltration), gastric glandular atrophy on the basis of gland loss, and intestinal metaplasia.

**Measurement of lipid peroxides and myeloperoxidase**

Gastric mucosal samples were suspended in phosphate-buffered saline supplemented with 0.1% butylated hydroxytoluene and were frozen at –80°C until use. Later, tissue homogenates were prepared, and the concentration of the TBA-reactive substances was measured using the method of Ohkawa \textit{et al.} [12] as an index of lipid peroxidation. The level of TBA-reactive substances in the mucosal homogenates was quantified using a 1,1,3,3-tetramethoxypropane as the standard and expressed as nanomoles of malondialdehyde per mg protein. Total protein in the tissue homogenates was measured using the Lowry method [13]. The tissue homogenates were disrupted by ultrasonic sonication and centrifuged at 12,000 g for 15 min. MPO concentrations in the supernatant were measured by the enzyme immunoassay (EIA) method using a kit (MPO kit, Bioxytech, Portland, OR).

**Measurement of \textit{H. pylori} antibody**

\textit{H. pylori} antibody titers were measured by the HM-CAP method using a kit manufactured by Kyowo Medex Co., Ltd., Tokyo, Japan.

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**Table 2. Gastric mucosal injury score (modified Lanza score, MLS)**

| Grade 0 | No erosion/hemorrhage |
| Grade 1 | Erosion and hemorrhage are localized in one area of the stomach; <2 lesions. |
| Grade 2 | Erosion and hemorrhage are localized in one area of the stomach; 3–5 lesions. |
| Grade 3 | Erosion and hemorrhage appear in two areas in the stomach. Although there are <10 erosions in the whole stomach, one area involves >6 erosions. |
| Grade 4 | Erosion and hemorrhage appear over three or more areas in the stomach. |
| Grade 5 | Gastric ulcer |

Lanza score was partially modified by the criteria of Kobayashi and Mizushima [25].
Measurement of indomethacin blood concentration

Blood samples were collected 12 h after the final administration of trial medications, and serum concentration of indomethacin was measured by the high-performance liquid chromatography method.

Safety parameters

Adverse events occurring during the study were assessed for their relationship to the study drug classified as "not related", "unlikely", "likely", or "definitely" related. The following laboratory parameters were evaluated at baseline and after treatment; hematology: erythrocytes, leukocytes, thrombocytes, hematocrit, and hemoglobin; biochemical: sodium, potassium, BUN, creatinine, total cholesterol, triglycerides, glucose, total bilirubin, asparate aminotransferase (AST), alanine aminotransferase (ALS), gamma-glutamyl transpeptidase (γ-GT), and alkaline phosphatase (ALP); urine analysis: protein, blood cells, and glucose.

Statistical analysis

The incidence of symptoms and gastric lesions of two groups were compared by using Fisher’s exact probability test. One-way analysis of variance (ANOVA) with Scheffe’s multiple comparison test was performed when more than two groups were compared. Differences in indomethacin concentration were determined by Student’s t test. Differences were considered to be significant if the p value was less than 0.05. All analyses were performed using the Stat View 5.0-J program (Abacus Concepts, Inc., Berkeley, CA) on a Macintosh computer.

Results

Symptoms

In the rebamipide group, 7 of 12 cases (58%) developed subjective symptoms, while 9 of 12 cases (75%) in the famotidine group developed (Table 3). However, no significant difference was seen between the two groups (Fisher’s exact probability test: p = 0.333). Epigastralgia, abdominal fullness, and diarrhea are major symptoms in both groups. The severity rating was mild to moderate for all complaints, and there were no serious complications that resulted in stopping medication in this study.

Gastric mucosal injury

The incidence of gastric lesions (MLS 2 or higher) was 17% (2/12) in the rebamipide group and 25% (3/12) in the famotidine group (Fisher’s probability test: p = 0.333). Gastric ulcer did not occur in both groups.

Lipid peroxides and MPO concentrations in the gastric mucosa

Gastric concentrations of TBA-reactive substances and MPO tended to increase after the treatment (Table 5, 6). However, there were no significant differences among three groups by the ANOVA.

Blood indomethacin concentration

Serum indomethacin concentrations were 112.5 ± 21.4 ng/ml in the rebamipide group and 124.8 ± 28.4 ng/ml in the famotidine group, showing no significant difference between the groups.

Safety parameters

No abnormal test values were noted in both groups.

Discussion

The present study described here is the first to compare rebamipide, a gastroprotective drug, with low-dose famotidine (20 mg/day) as prophylaxis against gastric injury and symptoms induced by indomethacin in H. pylori-negative healthy volunteers. We selected H. pylori-negative volunteers by measuring anti-H. pylori IgG antibody and also confirmed the normal gastric mucosa without inflammation.
or atrophy which was demonstrated by histological findings of gastric corpus and antral biopsies. The reason why we selected these subjects in the present study, is that it would be able to assess pharmaceutical efficacy for acute gastric mucosal injury induced by indomethacin precisely without being affected by H. pylori infection or background mucosal inflammation. The effect of H. pylori-infection on NSAIDs-induced gastropathy is still controversial. Meta-analysis has shown that H. pylori eradication reduces the incidence of peptic ulcer in the overall population receiving NSAIDs [14]. Nonetheless, H. pylori eradication seems less effective than treatment with a maintenance proton pump inhibitor for preventing NSAID-associated ulcers. In any event, the purpose of the present study is not to assess the influence of H. pylori infection on NSAID-gastropathy, but to compare the protective effects of two drugs, rebamipide and famotidine, against indomethacin-induced gastric mucosal injury in volunteers with non-inflammatory and non-atrophic gastric mucosa.

The primary end point of our study was to compare the incidence of gastric mucosal injury (MLS 2 or higher) after indomethacin administration. In our previous study which was conducted by the completely same protocol; indomethacin treatment (25 mg, t.i.d., 7 days) for healthy volunteers, gastric lesions were found in seven (70%) of the 10 subjects (Fig. 1) [9]. Gastric ulcers occurred in 3 subjects (30%). In contrast, the incidence of gastric lesions and ulcers was 14% and 0%, respectively, in the rebamipide group. In the present study, the incidence of gastric lesions was 17% in the rebamipide group and 25% in the famotidine group, respectively. There was no significant difference between two groups. No gastric ulcers occurred in both groups. Since there was no difference in the serum indomethacin concentration between the groups, it is clear that the protective effects of these drugs on the gastric mucosa is not mediated through changes in the absorption of indomethacin. Since rebamipide does not inhibit gastric acid or pepsin secretion [15], it may prevent gastric injury by affecting the gastric mucosal defense system. Although many reports have demonstrated that rebamipide can reduce indomethacin-induced gastric mucosal injury in murine models [16–18], the present study reconfirmed its cytoprotection in human. Clinical trials have also reported that famotidine at high dosages provides preventive actions for NSAIDs-associated gastric injury [19, 20]. This is a first report showing that low-dose famotidine is effective for preventing indomethacin-induced gastric injury in Japanese healthy volunteers. These data suggest that rebamipide and famotidine are equally effective for prevention of acute gastric mucosal injury induced by indomethacin in H. pylori-negative healthy volunteers without a particular risk factor. Interestingly, a recent randomized, multicenter, controlled trial showed that the rebamipide prevented NSAID-induced peptic ulcer as effectively as misoprostol in patients on long-term NSAID therapy [27]. These data including the present data indicate that rebamipide may be a useful candidate to prevent NSAID-induced gastric injury in patients as well as healthy subjects.

To investigate the mechanism of cytoprotection by two drugs, tissue levels of lipid peroxides and neutrophil in the gastric mucosa were measured. The reason why we measured these parameters in the present study is due to accumulated evidence that lipid peroxidation mediated by oxygen radicals derived from activated neutrophil play a crucial role in the pathogenesis of NSAID-induced gastro-

| Table 5. Effects of rebamipide or famotidine on the gastric mucosal levels of lipid peroxides after the indomethacin treatment |
|---------------------------------------------------------------|
| (n = 12) | TBA-reactive substances (nmol/mg protein) | Antrum | Body |
| Before treatment | 0.98 ± 0.12 | 1.12 ± 0.34 |
| Rebamipide group | 1.11 ± 0.07 | 1.38 ± 0.16 |
| Famotidine group | 1.23 ± 0.14 | 1.47 ± 0.19 |

Each data indicate mean ± SE of 12 subjects.

| Table 6. Effects of rebamipide or famotidine on the gastric mucosal neutrophil accumulation after the indomethacin treatment |
|---------------------------------------------------------------|
| (n = 12) | MPO content (ng/mg protein) | Antrum | Body |
| Before treatment | 2.73 ± 1.32 | 2.46 ± 0.80 |
| Rebamipide group | 9.24 ± 3.49 | 6.31 ± 2.67 |
| Famotidine group | 7.17 ± 3.31 | 4.14 ± 1.20 |

Each data indicate mean ± SE of 12 subjects.

Fig. 1. Incidence of indomethacin-induced gastric lesion in Helicobacter pylori-negative healthy volunteers.
pathy [2, 3, 22, 23]. The present data showed the inhibitory tendency of these parameters by both drugs, however, there was no statistical significance among groups. To confirm the mechanism of these drugs, it will be needed to increase sample number in a future study. Recent study have demonstrated that the decrease in gastric mucosal blood flow is associated with NSAID-induced gastric mucosal injury, and rebamipide may have prevented NSAID-induced gastric mucosal injury by maintaining GMBF in healthy subjects [24].

The secondary end point of our study was to compare the incidence of subjective symptoms after indomethacin administration. In terms of the incidence of subjective symptoms, 58% of the subjects in the rebamipide group developed symptoms including epigastralgia, abdominal fullness, and diarrhea. Similarly, 75% of the subjects in the famotidine group developed similar symptoms. There was no significant difference between two groups and there were no serious complications that resulted in stopping medication during 7 days. Since previous studies have not demonstrated a correlation between symptoms and endoscopic findings in patients with NSAID-induced gastric mucosal injury, it was important to assess the effects of these drugs on the endoscopic findings. However, NSAID-induced these dyspepsia may lead to discontinuation of treatment in 5%–15% in the clinical field. Therefore, it may be also important to reduce the dyspeptic symptoms induced by NSAID. In a future study, it will be necessary to evaluate subjective symptoms in addition to endoscopic findings especially in a long-term use of NSAIDs.

In conclusion, we firstly demonstrated that rebamipide and famotidine is equally effective in the prevention of indomethacin-induced gastric injury in healthy volunteers. These data recommend rebamipide (100 mg, t.i.d.) or famotidine (10 mg, b.i.d.) for the prevention of acute gastric injury induced by NSAID in patients without a particular risk factor.

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