Determination of the adequate dosage of rebamipide, a gastric mucoprotective drug, to prevent low-dose aspirin-induced gastrointestinal mucosal injury

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Abstract

Small intestinal mucosal injury caused by low-dose aspirin (LDA; 100 mg) is a common cause of obscure gastrointestinal bleeding. We aimed to investigate the protective effects and optimal dose of rebamipide for low-dose aspirin-induced gastrointestinal mucosal injury. In this prospective randomized trial, 45 healthy volunteers (aged 20-65 years) were included and divided into three groups. The groups received enteric-coated aspirin 100 mg (low-dose aspirin) plus omeprazole 10 mg (Group A: proton pump inhibitor group), low-dose aspirin plus rebamipide 300 mg (Group B: standard-dose group), or low-dose aspirin plus rebamipide 900 mg (Group C: high-dose group). Esophagogastroduodenoscopy and videcapsule endoscopy were performed, and the fecal occult blood reaction and fecal calprotectin levels were measured before and two weeks after drug administration. Although the fecal calprotectin levels increased significantly in Group A, they did not increase in Groups B and C. The esophagogastroduodenoscopy and video capsule endoscopic findings and the fecal occult blood test findings did not differ significantly among the three groups. In conclusion, standard-dose rebamipide is sufficient for preventing mucosal injury of the small intestine induced by low-dose aspirin, indicating that high-dose rebamipide is not necessary.

Key Words: rebamipide, low-dose aspirin, gastrointestinal mucosal injury, fecal calprotectin, capsule endoscopy

Long-term use of low-dose aspirin (LDA; 100 mg) is associated with the development of peptic ulcers, and deaths due to these peptic ulcers have been reported.1-6 For prevention of LDA-induced gastrointestinal mucosal injury, proton pump inhibitors (PPIs) are the first-choice drug according to several guidelines.7-11 However, gastric acid suppressants, like proton pump inhibitors and histamine H2-receptor antagonists, do not prevent small intestinal mucosal injury because there is no acid in the intestine. In recent years, the gastrointestinal mucosal injury induced by LDA has attracted attention not only in the upper gastrointestinal tract but also in the lower gastrointestinal tract, and Lanasa et al.12 reported that LDA was associated with increased risk of both upper and lower gastrointestinal bleeding.

Several gastric mucoprotective drugs other than PPIs have been found to prevent LDA-induced small intestinal mucosal injury to some degree,13-18 however, one study found no preventive effect of such drugs on LDA-induced small intestinal mucosal injury.19 Of note, in the aforementioned reports, the dosages of gastric mucoprotective drugs were those recommended for the treatment of gastric/duodenal ulcers, the so-called “standard dosage”. However, these recommended dosages have not been firmly established to be adequate for the small intestine as well. It can be speculated that high-dose gastric mucoprotective drugs are more effective for the small intestine, although no trials on whether high doses of gastric mucoprotective drugs are necessary for preventing small intestinal mucosal injury have yet been reported.

Rebamipide, 2-(4-chlorobenzylamino)-3-[2(1H)-quinolinone-4-yl] propionic acid (Otsuka Pharmaceutical Co., Tokyo, Japan) is a gastric mucoprotective drug that stimulates the production of prostaglandins and epidermal growth factor, thereby preventing Helicobacter pylori-elicited neutrophil-induced mucosal injury and decreasing free radicals levels.20-22 Clinically, the efficacy against non-steroidal anti-inflammatory drug (NSAID)-induced gastric mucosal injury has been reported to be comparable to that of famotidine (10 mg twice a day), a histamine H2-receptor antagonist,23 with an effective dose of 300 mg (standard dose) of rebamipide for preventing LDA-induced gastroduodenal mucosal injury.24 A few clinical trials have investigated the effects of rebamipide (300 mg/day) plus PPIs vs placebo plus PPIs. There were a few reports on the protective effects of rebamipide against NSAID-induced small intestinal mucosal injury.17,24 However, the required dosage of rebamipide for effective prevention of LDA-induced small intestinal mucosal injury is unclear, with 900 mg being the maximum safe dose of rebamipide, as confirmed in a phase I study.25 In addition, Wallace et al.26 reported that PPIs exacerbate NSAID-induced small intestinal mucosal injury. There are currently no reported studies comparing rebamipide and PPIs directly for the prevention of LDA-induced gastrointestinal mucosal injury.

Based on the above reports, we devised this clinical study with the aim of comparing the efficacy in three groups (300 mg of rebamipide, 900 mg of rebamipide, and 10 mg of omeprazole) for the prevention of LDA-induced mucosal injury from the esophagus to the small intestine.

Methods

Subjects. The study was conducted prospectively at Osaka Medical College Hospital. Subjects eligible for inclusion were healthy adults who: 1) were aged between 20 and 65 years at the time of providing consent, 2) had freely provided informed consent.

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vascular diseases.

The present study was a prospective, randomized trial comparing the effects of a PPI and two dosages of a gastric mucoprotective drug on the esophagus, stomach, duodenum, small intestine, and colon. The subjects (n = 45) were divided into three groups (Groups A, B, and C; n = 15 each) and instructed to take the study drugs as directed for two weeks. Group A [the control (PPI) group] received low-dose (100 mg) enteric-coated aspirin (LDA) once a day plus omeprazole 10 mg once a day, Group B (standard-dose) received LDA plus rebamipide 300 mg (100 mg three times a day), and Group C (high-dose) received LDA plus rebamipide 900 mg (300 mg three times daily). The dosage of aspirin was determined based on the dosage recommended for antithrombotic activity in cardiovascular and cerebrovascular diseases. In Japan, the dosage of a PPI used for the prevention of LDA-induced gastric ulcers is half the dosage used for the treatment of gastric ulcers. On this basis, we determined that the appropriate dosage of omeprazole should be 10 mg/day. Both esophagogastroduodenoscopy (EGD) and video capsule endoscopy (VCE) were performed before and two weeks after drug administration. In addition, we measured the fecal occult blood reactions and fecal calprotectin levels of the subjects before and two weeks after to assess the level of inflammation in the lower gastrointestinal mucosa (Fig. 1).

Sample size. The sample size was calculated based on the results of a review of the incidence of NSAID-induced small intestinal mucosal injury examined by capsule endoscopy. According to several studies, the rate of NSAID-induced small intestinal mucosal injury ranges from 50 to 70%. Furthermore, Niwa et al. previously investigated the use of rebamipide for NSAID-induced small intestinal mucosal injury, and reported that the incidence of mucosal injury in the placebo and rebamipide groups was 80% and 20%, respectively. Assuming that omeprazole, which was employed as the control agent in this study, does not influence the small intestinal mucosa, the incidence of LDA-induced small intestinal mucosal injury in the omeprazole and rebamipide groups was estimated to be 70% and 20%, respectively. The number of patients required for each group to reach a significance level (paired) of 5% and detection power of 80% was 14.3, which was determined using the chi-square test; therefore, we enrolled 15 patients in each group.

Randomization. A coordinator performed a simple fixed-allocation randomization using a block-randomization scheme. Random numbers were generated by SAS software (SAS Institute, Cary, NC).

Evaluation of small intestinal lesions by VCE findings. Evaluation of small intestinal lesions was performed using a PillCamSB2 (Given Imaging, Yokneam, Israel), a VCE device specifically designed for the small intestine, after pre-treatment using the method described by Nouda et al. The subjects received 1 L of polyethylene glycol solution (Niflec; Ajinomoto Pharma Co., Ltd., Tokyo, Japan) containing 200 mg of dimethylpolysiloxane (Baros; Horii Pharmaceutical Ind., Ltd., Osaka, Japan) over one hour starting at 6:00 a.m. on the day of the examination, which was followed by VCE at 9:00 a.m. The small intestine was examined 8 h after capsule administration. Images were analyzed using RAPID Reader 6.5 software (Given Imaging).

The investigators responsible for evaluating the results of the capsule endoscopy of the small intestine were required to attend a standardized training session on the use of the Given Diagnostic System. These two investigators (S.N., T.K.) independently assessed the capsule endoscopic images under blinded conditions. If the observers recorded different findings, they discussed the case until an agreement was reached.

We evaluated the small intestinal mucosal injury based on the presence and degree of bleeding, erythema, erosions, ulcers, and stenosis. Erythema was defined as a red region with a border according to several studies, the rate of NSAID-induced small intestinal mucosal injury ranges from 50 to 70%. Therefore, we enrolled 15 patients in each group.

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We evaluated the small intestinal mucosal injury based on the presence and degree of bleeding, erythema, erosions, ulcers, and stenosis. Erythema was defined as a red region with a border extending from the peripheral normal mucosa, erosion as a defect in the normal villus mucosa, and ulcers as mucosal defects.
covered with a white coat based on the classifications reported by Fujimori et al. and Niwa et al. with slight modifications. Additionally, inflammatory changes in the small intestinal mucosa were evaluated using the Lewis score. The modified Lanza score (MLS) for the gastroduodenal mucosal injury. We evaluated the improvement rate of reflux esophagitis and the degree of gastric mucosa atrophy (Kimura-Takemoto classification) between the groups (Table 1). Furthermore, the time required for the VCE to pass through the stomach and small intestine was almost identical in the three groups (Table 2).

**Evaluation of upper gastrointestinal lesions using EGD.** We evaluated the improvement rate of reflux esophagitis and the degree of gastric mucosa atrophy (Kimura-Takemoto classification) between the groups (Table 1). Furthermore, the time required for the VCE to pass through the stomach and small intestine was almost identical in the three groups (Table 2).

**Evaluation of upper gastrointestinal lesions before and two weeks after drug administration.** There were no significant differences in the prevalence rates of reflux esophagitis among the three groups both before and two weeks after drug administration (Fig. 2). Changes in the MLS following drug administration determined by EGD in each group are shown in Fig. 3. There were no significant differences in the rate of worsening of the MLS between the groups; however, there was a trend toward improvement in MLS scores in the treatment groups, which became more evident as the dosage of rebamipide increased: Group A vs B: \( p = 0.651 \), B vs C: \( p = 0.224 \), and A vs C: \( p = 0.100 \). One subject in Group B did not undergo the second EGD.

**Evaluation of small intestinal lesions before and two weeks after drug administration.** There were no significant differences in the numbers of small intestinal lesions in each group before and two weeks after drug administration (Table 3). Fig. 4 shows typical capsule endoscopic views of the small intestinal mucosal injuries observed in this study. Bleeding and stenosis were not found in any subject.

**Evaluation of fecal calprotectin levels in each group before and two weeks after drug administration.** The fecal calprotectin levels in Group A worsened two weeks after drug administration (from 2,665 ± 4,245 at baseline to 22,192 ± 32,481 ng/g post-treatment; Table 2: Capsule endoscope transit times (min)

| Characteristic                  | Group A (n = 15) | Group B (n = 15) | Group C (n = 15) | \( p \)  
|---------------------------------|------------------|------------------|------------------|------
| Stomach Baseline                | 69.3 ± 59.1      | 57.2 ± 88.2      | 35.1 ± 31.1      | NS   
| Post-treatment                  | 53.6 ± 45.5      | 39.9 ± 31.8      | 37.3 ± 41.0      | NS   
| Small intestine Baseline        | 199.8 ± 108.8    | 223.8 ± 91.9     | 145.7 ± 90.1     | NS   
| Post-treatment                  | 219.6 ± 67.7     | 224.9 ± 84.1     | 193.5 ± 88.5     | NS   

Data are presented as the mean ± SD. NS, not significant.
whereas those in Groups B and C remained unchanged (from 5,785 ± 8,316 to 7,781 ± 14,754 ng/g; \( p = 0.844 \) and from 5,877 ± 11,168 to 2,484 ± 4,197 ng/g; \( p = 0.438 \), respectively) (Fig. 5).

Presence of fecal occult blood before and two weeks after drug administration. There were no significant differences in the presence of fecal occult blood before and two weeks after drug administration in any of the groups (Table 4).

**Discussion**

This study revealed that 300 mg of rebamipide can prevent LDA-induced small intestinal mucosal injury with an efficacy similar to that of 900 mg in healthy volunteers. Certainly, there were no significant differences in the prevalence rates of lesions in the upper gastrointestinal tract among the three groups at two weeks after drug administration.

The main effect of LDA is suppression of cyclooxygenase-1 activity, and it is believed that the mechanism of LDA-induced small intestinal mucosal injury is similar to that of other NSAIDs, which also involves suppressing cyclooxygenase activity. The pathology and prophylaxis of NSAID-induced small intestinal mucosal injury have recently been investigated in animal models. It has been speculated that NSAID-induced small intestinal

**Fig. 2.** Esophageal lesions. There were no significant differences in the improvement rate of reflux esophagitis among the three groups.

**Fig. 3.** Gastroduodenal lesions. No significant differences in the rate of modified Lanza score worsening were observed. However, there was a trend toward prevention of low-dose aspirin-induced mucosal injuries in the stomach/duodenum in the rebamipide groups, and this tendency was dose-dependent, with a stronger response observed with high-dose rebamipide. NS, not significant.

| Table 3. The average numbers of small intestinal lesions before and two weeks after drug administration (paired t test) |
|---------------------------------------------------------------|
| **Small intestinal lesions**                  | **Baseline (mean ± SD)** | **Post-treatment (mean ± SD)** | **p** |
| Group A Omeprazole 10 mg (n = 15)               |  |  |  |
| Erythema                                      | 1.5 ± 1.685               | 2.7 ± 4.818               | 0.247 |
| Erosion                                       | 0.2 ± 0.775               | 2.9 ± 7.049               | 0.167 |
| Ulcer                                         | 0 ± 0.000                 | 0.5 ± 1.060               | 0.110 |
| Group B Rebamipide 300 mg (n = 15)             |  |  |  |
| Erythema                                      | 0.8 ± 1.320               | 2.3 ± 3.411               | 0.087 |
| Erosion                                       | 0.2 ± 0.561               | 1.4 ± 2.444               | 0.095 |
| Ulcer                                         | 0 ± 0.000                 | 0.2 ± 0.775               | 0.334 |
| Group C Rebamipide 900 mg (n = 15)             |  |  |  |
| Erythema                                      | 1.3 ± 2.225               | 2.1 ± 4.758               | 0.408 |
| Erosion                                       | 0 ± 0.000                 | 0.8 ± 1.612               | 0.075 |
| Ulcer                                         | 0 ± 0.000                 | 0.1 ± 0.352               | 0.164 |

Data are presented as the mean ± SD.
mucosal injury occurs due to reduced production of prostaglandins, which in turn causes microcirculatory disturbance by reducing mucus production and accelerating peristalsis, and this activates inflammatory cytokines resulting in mucosal injury. In addition, it has been reported that enterobacteria may cause inflammation via Toll-like receptor-4.\(^{(37)}\)

The use of gastric mucoprotective drugs for the prevention of NSAID- or LDA-induced small intestinal mucosal injuries has been evaluated in several studies. Gastromucoprotective drugs can be classified as effective\(^{(9–11,13–17,24,28)}\) or ineffective\(^{(19)}\) in preventing NSAID- or LDA-induced small intestinal mucosal injury. Each drug has already been proven to prevent NSAID- or LDA-induced small intestinal mucosal injury in animal models. However, the results of these studies are insufficient to confirm that the ineffective drug is indeed ineffective in preventing small intestinal mucosal injury because the dosages used in these studies were those used for treating gastric ulcers. By increasing the dosage, a gastromucoprotective effect may have been obtained. However, the appropriate dosage of gastromucoprotective drugs for the prevention of small intestinal mucosal injuries is not yet known. Therefore, we investigated the protective effects and optimal dosage of rebamipide for LDA-induced gastrointestinal mucosal injury. There are no studies comparing high-dose with standard-dose rebamipide for the prevention of LDA-induced small intestinal mucosal injury, although the dosage to treat gastric ulcers may be sufficient to prevent LDA-induced small intestinal mucosal injury.

There are a few reports regarding rebamipide use in the prevention of NSAID- or LDA-induced gastrointestinal mucosal injury. Fujimori \textit{et al.}\(^{(38)}\) reported that the combination of 300 mg rebamipide and 20 mg omeprazole has higher potential for reducing the injury severity of diclofenac sodium-induced small intestinal mucosal injury than 20 mg of omeprazole alone. How-

![Fig. 4. Representative video capsule endoscopy findings of small intestinal mucosal injuries after treatment.](image)

**Fig. 4.** Representative video capsule endoscopy findings of small intestinal mucosal injuries after treatment.

**Fig. 5.** Fecal calprotectin levels before and after treatment. A significant increase in the fecal calprotectin levels was observed between baseline and post-treatment in Group A \(p = 0.004\). Conversely, there were no significant differences in the calprotectin levels between the baseline and post-treatment in Group B \(p = 0.844\) or Group C \(p = 0.438\).
ever, some analyses in their study were inappropriate: The two groups were compared without excluding the obvious outliers. Their study does not provide conclusive evidence for the preventive effect of rebamipide against NSAID-induced small intestinal injury. Mizukami et al.\(^{(17)}\) reported that the preventive effect of rebamipide plus omeprazole was significantly higher than that of placebo plus omeprazole; however, their study did not confirm the damaging effect of omeprazole on the small intestine. In the present study, the standard dosage of rebamipide significantly inhibited the onset of small intestinal mucosal injuries as well as that with high dose. On the contrary, Watanabe et al.\(^{(19)}\) reported 900 mg of rebamipide, not the standard dosage one, was necessary to treat LDA-induced moderate-to-severe small intestinal mucosal injury.

The mechanisms underlying the effect of rebamipide on the small intestine are not clear. The effect of rebamipide in the small intestine could be the same as that in the stomach: increasing mucus secretion and scavenging free radicals. Recently, Tanigawa et al.\(^{(40)}\) reported that intestinal microbiota modulation by up-regulation of \(\alpha\)-defensin 5 by rebamipide might be one of the mechanisms underlying its preventive effect against NSAID-induced small intestinal mucosal injury. Kurata et al.\(^{(41)}\) reported that rebamipide regulates the small intestinal microbiota, in particular decreasing the number of \(\text{Enterobacteriacae}\) induced by indomethacin administration, and decreases the gene expression of TNF\(\alpha\) and Duox2 upregulated by indomethacin treatment.

Calprotectin is a major protein of the neutrophil cytoplasm, and the amount of fecal calprotectin reflects the degree of inflammation of the lower digestive tract and is a highly sensitive and specific marker for inflammatory bowel diseases.\(^{(35,42)}\) The difference in the degree of LDA-induced small intestinal injury observed upon capsule endoscopy is unclear, owing to the fact that LDA does not cause as significant of a gastrointestinal mucosal injury as other NSAIDs. Hence, it is necessary to measure the calprotectin levels to clarify the difference in the degree of LDA-induced small intestinal injury. Accordingly, we verified LDA-induced gastrointestinal mucosal injury biochemically by measuring fecal calprotectin. We found that, while the fecal calprotectin levels increased in the PPI group, they did not increase in the rebamipide groups suggesting that the PPI did not prevent LDA-induced small intestinal mucosal injury. However, the presence of fecal occult blood, another well-established marker for colonic mucosal injury, was not significantly different between the groups.

We previously reported that capsule endoscopic findings correlated with fecal calprotectin levels in two studies using diclofenac sodium 75 mg.\(^{(9,10)}\) In these two reports, the mean number of small intestinal mucosal injuries by capsule endoscopy and fecal calprotectin levels per subject who took diclofenac sodium 75 mg plus omeprazole 10 mg, or famotidine 20 mg for two weeks, increased significantly. In the present study, although there were no significant differences in the capsule endoscopic findings between the three groups, there was a significant increase in the fecal calprotectin levels in the PPI group between baseline and post-treatment, which was not seen in the standard- or high-dose rebamipide groups. There are two possibilities. One is that mucosal injury induced by LDA may be milder than that by diclofenac sodium. The other is that the fecal calprotectin levels may have a higher sensitivity than endoscopic findings. In the present study, VCE revealed no significant differences between the groups and the fecal calprotectin level was significantly higher in the PPI group than in the standard- and high-dose rebamipide groups.

This study has some important limitations, including the short duration, the inclusion of healthy volunteers, and the lack of colonoscopic evaluation. Accordingly, large-scale, long-term, prospective studies in different patient populations are warranted to confirm our results.

In conclusion, the present study revealed that both 300 mg and 900 mg of rebamipide were superior to 10 mg of omeprazole for preventing LDA-induced small intestinal mucosal injury. Based on these findings, we recommend that long-term LDA users without a history of peptic ulcers or gastrointestinal bleeding should be simultaneously treated with 300 mg of rebamipide instead of a PPI for total gastrointestinal management. High-dose rebamipide, such as 900 mg, is not necessary for preventing LDA-induced gastrointestinal mucosal injury.

**Conflict of Interest**

KH has received research grants and speaker’s fees from Otsuka Pharmaceutical Co., Ltd. The other authors declare no conflicts of interest associated with this manuscript.

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