Original Article

Efficacy of rebamipide for low-dose aspirin-related gastrointestinal symptoms

Kazuhiro Mizukami,* Kazunari Murakami, Yuka Hirashita, Akari Hisamatsu, Ryo Ogawa, Masahiro Uchida, Yoshifumi Nakagawa, Tadayoshi Okimoto, Masaaki Kodama and Toshio Fujioka

Departments of Gastroenterology, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hasamamachi, Yufu, Oita 879-5593, Japan

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Gastrointestinal symptoms are a problematic issue for patients who take low-dose aspirin for long time. We conducted a pilot study to investigate the efficacy of combination therapy with proton pump inhibitor and rebamipide. This was a prospective, randomized, double-blind, placebo-controlled cross-over study. All the subjects received aspirin 100 mg and omeprazole 20 mg. The subjects were divided into two groups and received either rebamipide 300 mg or placebo, which was prescribed for 4 weeks. The subjects were instructed to record their gastrointestinal symptom rating scale before the study and 1 and 4 weeks after beginning the protocol. These scores of the groups were compared before and after the treatment to evaluate the severity of their symptoms and the number of symptom items present in each group. For the subjects receiving rebamipide, the total prevalence of lower gastrointestinal symptoms was significantly different from the placebo group (p=0.0093) at week 4. No troublesome symptoms were observed in the rebamipide group. Inconclusion, the administration of rebamipide prevented the occurrence of troublesome symptoms, especially lower gastrointestinal symptoms, in patients taking aspirin and omeprazole. Rebamipide is a candidate drug for combination therapy with proton pump inhibitors to prevent low-dose aspirin-induced gastrointestinal symptoms.

***Key Words*: aspirin, symptoms, rebamipide, placebo, adaptation**

The chronic use of low-dose aspirin is increasing in patients with cardiac and cerebral diseases worldwide.[1] Although aspirin is a useful therapy for the management of these diseases, several adverse events related to its use are known to occur.[2] Aspirin-related gastrointestinal (GI) bleeding is the most serious of these adverse events. The quality of life (QOL) of patients on low-dose aspirin therapy is important because low-dose aspirin is usually associated with long-term use. The prevalence of GI symptoms is one problematic issue in patients who take low-dose aspirin. Cayla *et al.*[3] surveyed 8,106 patients on low-dose aspirin in France and found that one fifth reported upper GI symptoms. Proton pump inhibitors (PPIs) have been reported as the most useful therapy for aspirin-related GI problems. However, several reports have shown that 10–40% of patients with GERD do not respond to PPIs.[4,5] There are no other therapeutic options for these non-responding patients, and investigations into other possible therapeutic strategies are of prime importance. Therefore, studies on the effect of PPI in combination with other therapies are needed because of the current high prevalence of PPI administration.

Rebamipide (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) is an endogenous inducer of prostaglandins that is indicated for gastric ulcers and gastritis. Previous reports have indicated that rebamipide induces the production of intracellular prostaglandins,[6] improves blood flow,[7] suppresses increases in permeability,[8] scavenges free radicals,[9] and has an anti-inflammatory action.[10] Moreover, Tanigawa *et al.*[11] reported that the suppressive effect of rebamipide on non-steroidal anti-inflammatory drugs (NSAIDs) induced gastric mucosal injury can be attributed to reduced 15-hydroxyprostaglandin dehydrogenase expression, which increases the prostaglandin E2 concentration in the gastric tissue. In healthy subjects, rebamipide prevented endoscopic injuries and symptomatic disorders in patients on low-dose aspirin.[12–14] Chitapanarux *et al.*[15] reported that rebamipide improved the symptoms of chronic gastritis in patients with dyspeptic symptoms who did not respond to PPIs. Yoshida *et al.*[16] reported that a combination therapy with PPIs and rebamipide showed good efficacy in patients with recurring reflux symptoms during PPI maintenance therapy. Moreover, Yamamoto *et al.*[17] reported that patients taking rebamipide concomitantly with PPIs or histamine 2 receptor antagonists had mucosal injury less frequently than those taking acid suppressants plus other mucoprotective drugs.

In the present investigation, we conducted a pilot study to evaluate the effects of rebamipide for 4 weeks on low-dose aspirin-related symptoms in healthy subjects.

Materials and Methods

Healthy male subjects without symptoms before starting this study were eligible for inclusion. Subjects were excluded from the study if they showed active GI disorders, had used long-term aspirin or medication within 4 weeks prior to the study, or had a history of ulcers, surgery, or bleeding.

This study protocol was approved by the Ethics Committee of Oita University. All the subjects provided written informed consent prior to study entry.

Study design.

Treatment protocol. This was a prospective, randomized, double-blind, placebo-controlled, cross-over study, as shown in Fig. 1. The medication groups were defined as follows. The placebo group was given placebo plus 100 mg of aspirin (Bayer Pharmaceutical Co. Ltd., Tokyo, Japan) daily and 20 mg of omeprazole (Sawai Pharmaceutical Co. Ltd., Osaka, Japan) daily for 4 weeks, and the rebamipide group was administered 300 mg of rebamipide (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan), 100 mg of aspirin, and 20 mg of omeprazole daily for 4 weeks.

After 4 weeks, the treatment groups were switched, and each was given the other group's medications for an additional 4-week period. There was a 4-week washout period, all 3 medication were stopped, between the treatments. The washout period was set based on a previous study by Niwa.[18] The allocation and

*To whom correspondence should be addressed.
E-mail: mizkaz0809@oita-u.ac.jp

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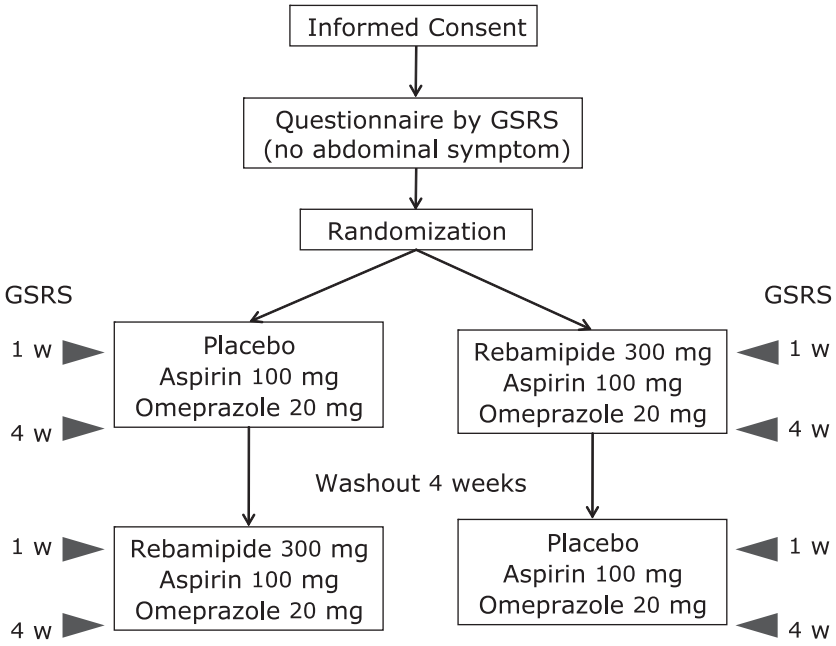

Fig. 1. Study design.

randomization procedures were conducted by an independent pharmacologist at Yamanami Pharmacy who had no connection to our institution or the results of this study. The placebo was prepared by that pharmacy.

Helicobacter pylori (*H. pylori*) status was evaluated using a rapid urine test (RAPIRAN® *H. pylori* antibody, Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) according the manufacturer's instructions.

Evaluation of symptoms (GSRS). The subjects were instructed to record their GI symptoms immediately before the study and at 1 and 4 weeks after beginning the protocol, using the gastrointestinal symptom rating scale (GSRS). The GSRS scores were compared before and after treatment to evaluate the severity and number of symptoms. The GSRS is a disease-specific instrument developed to evaluate common symptoms of gastrointestinal disorders, based on reviews of gastrointestinal symptoms and clinical experience.[19,20] The GSRS contains 15 items, each rated on a seven-point scale from no discomfort to very severe discomfort.[21] The 15 items are divided into two groups concerning the upper and lower GI tracts. The following 8 items concern the upper GI tract: abdominal pain, heartburn, acid regurgitation, hunger pains, nausea, borborygmus, abdominal distension, and eructation. The lower GI tract is investigated with the following 7 items: increased flatus, constipation, diarrhea, loose stools, hard stools, urgent need for defecation, and the feeling of incomplete evacuation. The GSRS scores were evaluated by counting the numbers of subjects with upper and/or lower GI symptoms. In addition, the number of symptoms present was calculated. The symptom severity was quantified by a seven-point Likert scale comprising the following levels: no discomfort at all, slight discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, severe discomfort, and very severe discomfort. The effect of rebamipide in preventing the progression of troublesome symptoms was analyzed. It was apparent that the effect of rebamipide was to prevent progressing troublesome. "Troublesome" was defined as moderate or severe discomfort on the symptom scale.

Endpoints. The primary endpoint was to evaluate of low-dose aspirin-induced GI symptom after 1 and 4 week in healthy subjects. The secondary endpoint was to evaluate the preventive effect of rebamipide.

Safety assessment. The subjects' symptoms were observed daily throughout the study period, and the information was evaluated by analyzing the patients' diaries.

Statistical analysis. Fisher's exact test was used to produce odds ratios and 95% C.I.s. to compare the placebo group with the rebamipide group. SAS ver 8.2 statistical software (SAS Institute, Cary, NC) was used for all analyses, and a p value <0.05 was considered statistically significant.

Results

Twelve healthy subjects (age range 24 to 43 years) were enrolled in the study. No subjects had *H. pylori* infection. In the placebo group, upper GI symptoms were developed in 5 subjects at one week, and lower GI symptoms were developed in 4 subjects at 1 week. At 4 weeks, 3 and 5 patients on placebo had upper and lower GI symptoms, respectively. In the rebamipide group, upper GI symptoms were induced in 3 subjects at 1 week, and 2 patients showed lower GI symptoms at 1 week. At 4 weeks, 1 patient had upper GI symptoms, and 1 had lower GI symptoms.

The number of items and the severity scale score for each item for subjects with symptoms in the placebo and rebamipide groups are given in Table 1. In the placebo group, troublesome symptoms including heartburn, abdominal distension and diarrhea were observed at 1 week, and troublesome diarrhea, loose stools and urgent need for defecation were observed at 4 weeks. There were no troublesome symptoms in the rebamipide group.

The comparison between the placebo and rebamipide groups for symptom items is summarized in Table 2. The number of symptomatic items in the placebo group was 10 at 1 week and 3 at 4 weeks for the upper GI tract and 8 items at 1 week and 10 at 4 weeks in the lower GI tract. The numbers of symptomatic items in the rebamipide group were 6 at 1 week and 1 at 4 weeks in the upper GI tract and 5 items at 1 week and 1 at 4 weeks in the lower GI tract. The total number of lower GI symptomatic items was 1 of 84 (84 results from 7 items multiplied by 12 subjects) in the rebamipide group, and this showed statistical significance com-

Table 1. Scale of items in subjects with symptoms between the placebo and the rebamipide group (n = 12)

Items of symptoms	Scales			
	Placebo		Rebamipide	
	1 week	4 week	1 week	4 week
Upper symptoms (8 items)				
Abdominal pains	2,2	—	2	—
Heartburn	6	—	2	—
Acid regurgitation	—	—	—	—
Hunger pains	2,2	—	2	—
Nausea	3	—	2	—
Borborygmus	2	2	2	2
Abdominal distension	3, 4, 6	3,3	2	—
Eructation	—	—	—	—
Lower symptoms (7 items)				
Increased flatus	2	—	2	—
Constipation	—	2,3	—	—
Diarrhea	2,4	2,4	2	—
Loose stools	2,2,2,3	2,2,2,4	2,2	2
Hard stools	—	—	2	—
Urgent need for defecation	3	4	—	—
Feeling of incomplete evacuation	—	2	—	—

Seven-point Likert scale: 1. No discomfort at all, 2. Slight discomfort, 3. Mild discomfort, 4. Moderate discomfort, 5. Moderately severe discomfort, 6. Severe discomfort, 7. Very severe discomfort.

Table 2. Comparison of the placebo and the rebamipide for symptom items in healthy subject with low-dose ASA (n = 12)

	Number of items in symptom scale					
	Placebo			Rebamipide		
	pre	1 week	4 weeks	pre	1 week	4 weeks
Upper (8 items)						
Number of items in troublesome	0	3	0	0	0	0
Total number of items	0	10	3	0	6	1
Lower (7 items)						
Number of items in troublesome	0	1	3	0	0	0
Total number of items	0	8	10	0	5	1
			p = 0.0093			
			Odds ratio: 0.08, 95% CI: 0.01–0.71			

8 items are abdominal pains, heartburn, acid regurgitation, hunger pains, nausea, borborygmus, abdominal distension, and eructation. 7 items are increased flatus, constipation, diarrhea, loose stools, hard stools, urgent need for defecation, and feeling of incomplete evacuation. Troublesome was defined as a symptom scale of moderate discomfort or more. Statistical analysis was performed by Fisher's exact test, compared with the placebo and the rebamipide group.

pared with the placebo group (odds ratio: 0.08, 95% CI: 0.01–0.71, $p = 0.0093$) at 4 weeks. No troublesome symptoms were observed in the rebamipide group.

Discussion

In the present study, low-dose aspirin induced upper GI symptoms in 5 subjects and lower GI symptoms in 4 patients at week 1 in the placebo group. At week 4, upper GI symptoms were present in 3 individuals and 5 patients had lower GI symptoms. It is well known that aspirin acts as a pain suppressor. However, our results show that aspirin-related symptoms were observed in nearly 40% of subjects. Moreover, almost 10% of subjects presented with troublesome symptoms, such as heartburn, abdominal distension, and diarrhea, despite taking PPIs (Table 1). Whereas the occurrence of upper GI symptoms at 4 weeks was reduced compared with that at 1 week, the lower GI symptoms did not show a similar decrease. Graham *et al.*[22] reported that mucosal adaptation by use of aspirin was observed. This adaptation was associated with less damage and with an accelerated healing process. Kawai *et al.*[12] also demonstrated in a recent endoscopic study that aspirin use resulted in adaptation. Our results may also suggest adaptation in terms of symptoms. However, this adaptation occurred for the upper GI-related symptoms but not for the lower GI symptoms. Nishida *et al.*[23] reported that the total number of lesions in the small bowel increased according to duration of low-dose aspirin administration. The reason for this difference is not clear, but we speculate that it may be due to differences between the upper and lower GI tracts in environmental conditions such as acid content, flora, and immune system variables.

However, we primarily investigated the preventive effect of rebamipide on aspirin-related GI symptoms. It is well known that PPIs are useful in the treatment of endoscopy-related upper GI damage and the resulting symptoms. However, PPIs have not

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been as effective in controlling lower GI damage and symptoms. Several studies have reported the efficacy of rebamipide treatment for lower GI symptoms. Niwa *et al.*[24] reported that rebamipide had a preventive effect on non-steroidal anti-inflammatory drug-induced small intestinal damage associated with the use of capsule endoscopy. In addition, Fujimori *et al.*[25,26] showed the usefulness of rebamipide and misoprostol in treating lower GI symptoms. Our group previously reported that rebamipide had a preventive effect in subjects with aspirin-induced small bowel injuries.[27] In the present study, the rebamipide group showed a total number of lower GI symptomatic items of 1 out of 84 possible, which was a statistically significant difference compared with the placebo group (odds ratio: 0.08, 95% CI: 0.01–0.71, $p = 0.0093$) at 4 week. Moreover, no troublesome symptoms were observed in the rebamipide group in either the upper or lower GI tract throughout the study period (Table 2). Kawai *et al.*[12] and Park *et al.*[28] reported that taking rebamipide prevented the GI symptoms that often result from low-dose aspirin and NSAIDs. Rebamipide has been shown to have preventive effects in both the upper and lower GI tracts. Moreover, Akamatsu *et al.*[29] showed that concentrations of rebamipide level in the jejunum was sufficient to protect for NSAID-induced gastrointestinal complications. Thus, rebamipide can be used to treat a wide breadth of GI symptom. Although PPIs are commonly used in patients with upper GI symptoms and injuries, lower GI complications may not respond to PPIs, likely due to the lack of acid in the small and large intestines. In addition, Gwee *et al.*[30] demonstrated that PPIs showed poor efficacy in patients with severe dyspeptic symptoms. Therefore, rebamipide is a candidate drug for use as a combination therapy with PPIs to treat low-dose aspirin-induced upper and lower GI tract symptoms. Patients are often administered low-dose aspirin over a span of multiple decades. Caution should be used in handling low-dose aspirin-related adverse events, particularly the endoscopic aspects (i.e., the prevalence of asymptomatic disorders, such as GI bleeding) and symptoms that can impact QOL. It is easy for patients to complete a questionnaire but not to be periodically examined by endoscopy. Troublesome symptoms with impacts on QOL are a major burden for patients. Therefore, the management of these symptoms is an important issue for them.

In conclusion, low-dose aspirin-induced upper and lower GI tract symptoms, including troublesome symptoms, were observed in patients despite their use of PPIs. The administration of rebamipide prevented these troublesome symptoms, especially their lower GI symptoms. Rebamipide is a candidate drug that could be used to prevent low-dose-aspirin-induced upper and lower GI tract symptoms as a combination therapy with PPIs.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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