Original Article

Circadian Variations of Gastrointestinal Mucosal Damage Detected with Transnasal Endoscopy in Apparently Healthy Subjects Treated with Low-Dose Aspirin (ASA) for a Short Period

—Prevention Trial, Randomized Double-Blind Placebo Controlled Preliminary Trial

Takashi Kawai¹, Tetsuya Yamagishi¹, and Shinya Goto²

¹Endoscopy Center, Tokyo Medical University Hospital, Tokyo, Japan

²Department of Medicine and Metabolic Disease Center, Tokai University School of Medicine, Tokyo, Japan

Aim: In this study, transnasal endoscopy was used to observe the time-course changes of gastrointestinal mucosa with low-dose aspirin (ASA), and the preventive effect of rebamipide was compared with placebo.

Methods: Twenty healthy *H.pylori*-negative subjects were divided between those receiving 100 mg aspirin with placebo, and those receiving 100 mg aspirin + 300 mg rebamipide for 7 days daily. Transnasal endoscopy was performed at 0, 2, 6 and 24 hrs on the first day, and then on the third and seventh days.

Results: Ulcers, in the duodenum at 24 hrs and in the antrum at 72 hrs, improved with continuous ASA. Erosions were mainly observed in the duodenum; erosions amounted to 14 at 3 days and 19 at 7 days in the placebo group. No ulcers and some erosions were mainly observed in the duodenum; erosions amounted to 5 at 3 days and 3 at 7 days in the rebamipide group.

Conclusion: In short-term gastrointestinal damage induced by ASA, damage was observed in the duodenum most frequently, and peak damage was at 24hrs and 72 hrs. Almost all damage improved gradually in spite of continuous ASA. Rebamipide reduced the damage of low-dose aspirin-induced GI complications.

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Key words; Low-dose aspirin, Transnasal endoscopy, Rebamipide, Prevention

Introduction

The action of ASA is derived from irreversible inhibition of the cyclooxygenase-1 enzyme, resulting in the inhibition of thromboxane A₂ formation, and the novel effects of ASA mediated by its salicylate moiety complement the role of the acetyl moiety in terms of its platelet inhibitory effect. The action of ASA resulted from interactions among platelet activa-

tion, endothelial inflammation/activation, and oxidative stress¹⁾.

The efficacy of low-dose ASA for secondary prevention of cardiovascular (CV) disease, such as the prevention of CV events in patients with a history of myocardial infarction, stroke, transient ischemic attack and stable angina, has been documented in several randomized trials and meta-analyses²⁻⁴⁾; however, there were no significant effects of the primary prevention of non-fatal stroke or CV death⁵⁾. The American Heart Association recommends that daily low-dose ASA should be used in persons with high coronary and stroke risk, and with 10-year risk of CV events of more than 10%⁶⁾; therefore, low-dose ASA has been widely used since it is a cheap and effective means of prevent-

Address for correspondence: Takashi Kawai, Endoscopy Center, Tokyo Medical University Hospital, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

E-mail: t-kawai@tokyo-med.ac.jp

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ing CV events. More than 50 million adults in the US are estimated to take ASA regularly for CV disease prevention⁷⁾, as are approximately 5 million Japanese. The trend in taking ASA to prevent CV disease is encouraging, since other risk factors, such as aging, diabetes, hypertension, and hypercholesterolemia, are increasing. Thus, the threshold for ASA administration in primary prevention has been controversial in Japan⁸⁾. Morimoto *et al.* analyzed differences in the epidemiology of atherosclerotic disease in subjects from Japanese and US populations, and predicted 5-year rates of coronary heart disease per 1,000 patients. This result was that only Japanese men with both hypertension and diabetes would benefit from ASA as a primary preventive measure⁹⁾; therefore, the results of American clinical trials or practice guidelines may be not applicable in Japan.

Despite its therapeutic benefits, ASA is associated with considerable upper gastrointestinal (GI) toxicity. Although low-dose ASA, defined as 75–325 mg daily, has fewer upper GI side effects than high-dose ASA and other non-steroidal anti-inflammatory drugs, the risk is still substantial¹⁰⁾. ASA acts to inhibit cyclooxygenase and suppress GI mucosal synthesis, which is one of the important mechanisms of mucosal damage by ASA¹¹⁾.

Recently, a case report was published in *Circulation*¹²⁾. The patient was hospitalized with acute coronary syndrome requiring emergency percutaneous coronary intervention with drug-eluting stents, and later returned to the Emergency Department with tarry stool. Endoscopy showed a bleeding duodenal ulcer. The administration of low-dose ASA has recognizable risks: GI complications such as ulceration and related bleeding. In addition, ACCF/ACG/AHA expert consensus in 2008 reported that the use of low-dose ASA (75–325 mg per day) was associated with a 2- to 4-fold increased risk of upper GI events. Gastroprotection strategies consist of the use of a proton pump inhibitor (PPI) in patients at high risk of GI bleeding with a history of ulcers¹³⁾. On the other hand, there is no evidence in epidemiological data of patients with low-dose ASA in Japanese populations. A large-scale study “Management of ASA-induced Gastrointestinal Complications” (MAGIC) was started and enrolled patients in Japan, and was registered at ClinicalTrials.gov (ID000000853). This study aimed to obtain a new indication for secondary prevention for patients with low-dose ASA-induced GI complications. These actions were to recognize GI risks for patients on low-dose ASA.

Most patients taking ASA develop an acute mucosal region, particularly relating to damage to the GI

mucosa, such as petechia and erosions. Although petechia and erosions are not clinically relevant, erosions may develop into ulcers and/or associated complications. Major GI complications are ulcers with bleeding and perforations, while minor GI complications are dyspepsia, erosions, erythema, and petechia. Yeomans *et al.* demonstrated that, among 187 patients receiving low-dose ASA for CV disease prophylaxis, the prevalence of endoscopically detected GI ulcers was 11% (95% CI; 6.3–15.1%)¹⁴⁾. Primary and secondary endpoints of numerous studies that evaluated the preventive effect of anti-ulcer agents for ASA-induced GI diseases were endoscopic evaluation, clinical outcome, and/or dyspepsia; however, these methods of evaluation have several problems. In many studies that set out to evaluate clinical outcome and dyspepsia, GI bleeding was not defined or was defined in vague terms. Moreover, patients who take ASA are asymptomatic, even if GI bleeding occurs. In addition, endoscopic evaluation is an uncomfortable, painful method that is difficult to perform with appropriate frequency, even though it is very useful for diagnosing and monitoring bleeding. Side-effects occur with the topical and systemic presence of ASA, so short-term observation for systemic presence by periodic endoscopic examination is needed. On the other hand, daily doses of 75 mg ASA virtually completely inhibit COX-1 within a few days. This suggests that there are GI injuries in the acute phase related with topical presence. There are few reports on ASA-induced GI injuries observed for a few days on initial administration, although several short-term studies conducted observations for a few weeks^{15, 16)}; therefore, very short-term observation by endoscopic examination is needed.

Recently, transnasal upper-gastrointestinal endoscopy has become popular. Transnasal, unsedated, upper-gastrointestinal endoscopy has been developed as an alternative to transoral endoscopy to reduce the cost as well as the risks associated with conscious sedation^{17, 18)}. In addition, transnasal upper GI endoscopy is a comfortable and imposes less stress due to sedation, such as respiratory depression, hypotension, paradoxical agitation, and anaphylaxis¹⁹⁾, and, most importantly, imposes less load on the cardiovascular pulmonary system²⁰⁾.

Lanas *et al.* demonstrated that several studies in the US and EU supported the risk for patients with low-dose ASA-associated upper GI side-effects. Furthermore, administration of PPI was the most effective therapy for the prevention and/or relief of such side-effects in at-risk patients^{21, 22)}. In particular, the use of PPI is sufficient for high risk groups, such as a history of GI ulceration; however, PPIs are expensive

Fig. 1. Study design.

for use in low-risk groups; therefore, candidate drugs other than PPIs that have the clinical efficacy and are cost effective are needed.

Rebamipide (2-(4-chlorobenzoylamino)-3-[2-(1H)-quinolinon-4-yl]-propionic acid) (Otsuka Pharmaceutical Co., Tokyo) is a mucosal-protective drug that has many biological effects in the gastric mucosa, such as increasing blood flow, increasing the biosynthesis of prostaglandins, and decreasing oxygen radical levels²³⁻²⁵. Rebamipide improved the digestive epithelial barrier by strengthening its integrity in normal and inflammatory conditions²⁶, and is efficacious in reducing gastric injury in healthy subjects taking ASA 1,500 mg once daily²⁷.

The aim of this study was to evaluate where, when, and what kind of mucosal damage is induced by low-dose ASA in a short-term period using transnasal endoscopy, and to evaluate the preventive effect of rebamipide for low-dose ASA-induced GI mucosal injury compared with a placebo.

Methods

A randomized, double-blind, placebo-controlled trial was performed in 20 healthy subjects. The study protocol was approved by the Ethics Committees of Tokyo Medical University Hospital, and written informed consent was obtained from all subjects.

Inclusion and Exclusion Criteria

Inclusion criteria were i) lack of gastric conditions such as bleeding or ulcer on endoscopy, and ii) *H. pylori* negativity on ¹³C urea breath test. Subjects who were taking other drugs were excluded.

Study Design

The study design was as shown in **Fig. 1**. Twenty healthy subjects were divided into two groups: those taking 100 mg ASA with a placebo or those taking 300 mg rebamipide. Both groups received their dose

three times daily for 7 consecutive days.

Transnasal endoscopy was performed at 0, 2, 6 and 24 hrs on the first day, and again on the third and seventh days.

All subjects were treated by a pharmacist at Tokyo Medical University Hospital and Tokyo University of Pharmacy and Life Science.

Randomization

Subjects were recruited for the treatment sequences in a random fashion according to a randomization schedule for the treatment period. A randomization number that was associated with a specific treatment, either rebamipide or placebo, was assigned to each subject in the study. Randomized numbers were generated by the SAS program.

Endpoints

The primary endpoint was to evaluate where, when, and what kind of mucosal damage is induced by ASA in a short-term period. The secondary endpoint was to evaluate the preventive effect of rebamipide in healthy subjects who took low-dose ASA compared with a placebo.

Measurement of Symptoms

The questionnaire to assess symptoms of abdominal pain used the Gastrointestinal Symptom Rating Scale (GSRS) throughout the study period. The GSRS is a self-administered questionnaire for assessing GI symptoms, and consists of 15 items²⁸. These include five subscales for reflux, abdominal pain, indigestion, diarrhea, and constipation. Abdominal pain was evaluated in this trial because of the character of the administered drug.

Evaluation Criteria

The categories of injury were erythema, erosions, petechia, and ulcers. Erythema was defined as a region clearly redder than surrounding mucosa, erosion as a

region with mucosal deficit, petechia as a bleeding region without mucosal deficit, and ulcer was defined as more than 5 mm. Gastric mucosal injuries detected on endoscopy were calculated among the erosions, erythema, petechia, and ulcers. The region of GI injury, such as the duodenum, antrum, angle, lower body, middle body, upper body, and fornix, was observed by transnasal endoscopy. All GI injuries were counted in each time course.

Erythema, erosions, petechia and ulcers were counted to compare low-dose ASA-induced GI injuries compared in the placebo and rebamipide groups. A deteriorated case was defined as a subject in whom the number of erosions, erythema, petechia, and ulcers increased by 2 or more compared with before the study, it was also defined as multiple injuries.

Endoscopic evaluation was performed by two endoscopists, blinded to the subject number and group. If the results differed, they were re-evaluated and discussed.

Evaluation of Adverse Events

The following GI symptoms and complications were to be recorded in the symptom diary for all subjects throughout the study period.

Statistical Analysis

Endoscopic gastric mucosal injuries were analyzed by Fisher's exact test. Findings of $p < 0.05$ were considered significant. Statistical analyses were performed using SAS® version 8.2 (SAS Institute, Cary, NC).

Results

Twenty healthy subjects were enrolled. The mean age of the subjects was 24 ± 4 years. Sixteen were male and four were female. No subjects were infected with *H. pylori*.

One case in the rebamipide group dropped out of this study due to epistaxis. The remaining 19 healthy subjects were divided into two groups: the low-dose ASA plus placebo group, and the low-dose ASA plus rebamipide group.

Short-Term Change of Gastric Mucosa by Administration of Low-Dose ASA in the Placebo Group

Time-course changes in the gastric mucosal region were measured by transnasal endoscopy in healthy subjects with low-dose ASA. The numbers of erosions, erythema, petechia, and ulcers are shown by time in each GI region (Table 1). Erosions were mainly observed in the duodenum; erosions amounted to 14

Table 1. Number of injuries in healthy volunteers with low-dose ASA according to region

	pre	2 hrs	6 hrs	24 hrs	3 days	7 days
Erosion						
Duodenum	0	0	0	0	7	13
Antrum	0	0	0	0	1	1
Angle	0	0	0	0	0	0
Lower body	0	0	0	0	3	0
Middle body	0	0	0	1	0	2
Upper body	0	0	0	2	2	3
Fornix	0	0	0	0	1	0
Total	0	0	0	3	14	19
Erythema						
Duodenum	0	2	0	13	10	10
Antrum	0	0	0	0	4	1
Angle	0	0	0	0	0	0
Lower body	0	0	0	1	0	6
Middle body	0	0	0	0	1	0
Upper body	0	2	3	5	5	12
Fornix	0	0	0	0	0	3
Total	0	4	3	19	20	32
Petechia						
Duodenum	0	0	1	4	24	14
Antrum	0	1	1	6	8	0
Angle	0	1	0	0	1	0
Lower body	0	1	0	2	3	0
Middle body	0	1	2	2	23	0
Upper body	0	2	9	5	7	15
Fornix	0	3	13	6	1	5
Total	0	9	26	25	67	34
Ulcer						
Duodenum	0	0	0	1	0	0
Antrum	0	0	0	0	1	0

at 3 days and 19 at 7 days. Two cases in which erosions increased are shown in Fig. 2. One case in which erosions were prevalent at 72 hrs and disappeared at 7 days in spite of continuous administration of low-dose ASA is shown in Fig. 3. Erythema was observed in the duodenum and upper body; erythema amounted to 19 at 24 hrs and increased to 32 at 7 days. Petechia was observed in the fornix in the early phase (at 6 hrs), and in the duodenum, antrum, and body at 3 days. Petechia amounted to 26, 25, 67, and 34 at 6 hrs, 24 hrs, 3 days, and, respectively 7 days. Ulcers, in the duodenum at 24 hrs and in the antrum at 72 hrs, were prevalent in one subject, shown in Fig. 4; however, the ulcers disappeared at 3 and 7 days, respectively in spite of continuous administration of low-dose ASA.

Fig. 2. Prevalence of gastric erosions at 7 days.

Endoscopic findings of serious erosions in two cases at 7 days (arrow heads).

Fig. 3. Progress of erosion in the duodenum of a healthy subject with only low-dose ASA.

Endoscopic findings of the erosions. In this case, erosion was recognized at 72 hrs, and disappeared at 7 days (arrow heads).

Fig. 4. Prevalence of duodenal and gastric ulcer.

Endoscopic findings of duodenum and gastric ulcer.

A: Ulcer in the duodenum at 24 hrs, B: Ulcer in the antrum of the stomach at 72 hrs (arrow heads).

Table 2. Comparison between placebo and rebamipide groups for healthy subjects by score of abdominal pain and nausea using GSRS

	Pre	2 hrs	6 hrs	24 hrs	3 days	7 days	Difference (delta in pre and worst score)
Placebo							
No. 1	3	3	3	5	3	5	+2
No. 2	3	3	3	3	11	3	+8
No. 3	6	6	5	7	6	5	+1
No. 4	3	5	5	4	3	3	+2
No. 5	3	3	3	3	3	4	+1
No. 6	11	8	9	9	7	7	-2
No. 7	5	3	3	3	3	3	-2
No. 8	3	3	4	3	3	3	+1
No. 9	3	3	3	3	3	3	0
No. 10	3	5	3	3	3	3	+2
Rebamipide							
No. 11	3	3	3	3	3	3	0
No. 12	3	3	3	3	3	3	0
No. 13	6	6	3	4	4	5	-1
No. 14	5	3	3	3	3	3	-2
No. 15	3	3	3	3	3	3	0
No. 17	3	3	3	3	3	3	0
No. 18	3	3	3	3	4	3	+1
No. 19	3	3	3	3	3	3	0
No. 20	3	3	3	3	3	3	0

Patients that worsened were 7 of 10 in the placebo group, and 1 of 9 in the rebamipide group ($p=0.0094$).

not have such induced adaptation and/or heat shock protein. Healthy subjects were enrolled in our present study because the objective was to investigate only the influence of ASA. Transnasal upper-gastrointestinal endoscopy is a useful technique for periodic monitoring. In our previous study, this system was used frequently. In this study, transnasal endoscopy was performed at 0, 2, 6 and 24 hrs on the first day, and then on the third and seventh day without pain or stress. In some patients it is not easy to insert through the nose because the cavity is narrow, and bleeding from the nose occurred in one subject. Treatment of this subject was stopped immediately, and the subject was managed until the bleeding stopped. Bleeding may be a risk of transnasal endoscopy, but it will be resolved by the development of new technology or thinner endoscopes. In 1999, Dumortier *et al.* reported a feasibility and tolerance trial by transnasal endoscopy. During this study, 82 of 100 (82%) transnasal endoscopies were feasible. The only side-effects observed were epistaxis (6 patients; 6%) and nasal pain (6 patients)¹⁶. One hundred seventeen transnasal endoscopies were examined in our trial for twenty subjects: only one subject dropped out due to epistaxis at 6 hrs on the

first day (0.9%). Epistaxis occurred in 6% in Dumortier's trial, but only 0.9% in our trial. Transnasal endoscopy is considered to be a safe monitoring system for chronic low-dose ASA users, although the physician may require a good technique and skill.

On the other hand, it is not possible to prevent GI complications in all cases of low-dose ASA use, such as by PPI therapy. PPIs inhibit the parietal cell proton pump, thus exerting a suppressive effect on gastric acid, and are only recommended for patients with ASA-induced GI injuries. More recently, the rate of recurrent ulcer bleeding was lower with esomeprazole in combination with ASA than with clopidogrel alone in patients with a history of ASA-associated ulcer bleeding³¹. Low-dose ASA-induced GI complications are asymptomatic, even though GI bleeding may occur. Endoscopic examination is the most important method of diagnosing and monitoring bleeding, and can also be used to cure bleeding.

In this study of healthy subjects, rebamipide showed efficacy as a candidate agent for low-dose ASA-associated gastric complications. Patients that showed worsened gastric mucosal erosions consisted of 1/9 (11.1%) in the rebamipide group, and 6/10 (60%) in

the placebo group. The rebamipide group showed a significantly higher preventive effect than the placebo group ($p=0.0274$); however, there was a limitation to our study: GI damage with low-dose ASA use is very slight, and serious ulcers and bleeding do not occur; however, the administration of ASA is certain to induce gastric mucosal injuries, even if slight. In this study, we used transnasal endoscopy, and observed short-term gastric mucosal changes on the endoscopic monitor. It is not known whether slight injuries, such as erosions, progress to serious problems. In the future, it will be important to investigate the relationship between slight gastric damage over a few days and serious bleeding. Recently, it was reported that rebamipide may have better preventive efficacy for NSAID-induced GI ulcers than misoprostol³²⁾. Although PPI is the most commonly used drug for patients with low-dose ASA induced GI complications, the result of our previous study may suggest the possibility of rebamipide as a candidate drug for *H.pylori*-negative patients.

Transnasal upper-gastrointestinal endoscopy may be indicated for patients who need periodical evaluation of the esophagus and gastro-duodenum due to the influence of several drugs, because the procedure does not cause pain or stress.

In conclusion, transnasal upper-gastrointestinal endoscopy is useful for frequent endoscopic examinations. Short-term administered low-dose ASA induced slight gastroduodenal injury, and these injuries were decreased at three days in spite of continuous low-dose ASA. Rebamipide may contribute to the primary prevention for patients with low-dose ASA-induced GI complications in *H.pylori*-negative patients. A large-scale, long-term trial is required to confirm this finding.

Disclosure

Prof. Goto has received honoraria and consulting fees from Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Kowa, Novartis, Otsuka, sanofi-aventis, Schering-Plough, and Takeda. Prof. Goto has also received research grants from Eisai, Ono, sanofi-aventis, AstraZeneca, Kowa, and Pfizer within the last three years.

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