Low-Dose Aspirin-Induced Gastroduodenal Mucosal Injury in Japanese Patients with Arteriosclerotic Disease

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Abstract

Background We aimed to elucidate the risk factors and preventive factors associated with chronic low-dose aspirin (L-ASA)-induced gastroduodenal mucosal injury in Japanese patients with arteriosclerotic disease.

Methods This retrospective observational study included 400 L-ASA users who underwent upper gastrointestinal endoscopy. We investigated patients' clinical characteristics, including age, peptic ulcer history, concomitant drugs [i.e. gastric agents, antiplatelet drugs, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids], abdominal symptoms, endoscopic findings, and interruption of L-ASA before endoscopy. The severity of gastroduodenal mucosal lesions was evaluated using the modified LANZA score (MLS).

Results Of 400 patients, 249 (62%) and 41 (10%) had gastroduodenal mucosal lesions (MLS ≥ 1) and gastroduodenal ulcers, respectively. Peptic ulcer history, abdominal symptoms, proton pump inhibitor (PPI), histamine type 2-receptor antagonists (H2RA), and the cessation of L-ASA before endoscopy were significantly associated with L-ASA-induced gastroduodenal ulcers; the odds ratio (OR) (confidence interval (CI)) was 5.49 (1.82-16.55), 4.56 (1.93-10.75), 0.12 (0.03-0.42), 0.13 (0.04-0.40) and 0.11 (0.04-0.29), respectively. Moreover, patients having two or more of five factors [i.e. advanced age (≥ 75), anticoagulants, antiplatelet drugs, NSAIDs and corticosteroids] had a significantly higher prevalence of L-ASA-induced gastroduodenal ulcers [OR (CI): 2.39 (1.002-5.69)].

Conclusion Peptic ulcer history, abdominal symptoms and the summation of risk factors increased the risk for L-ASA-induced gastroduodenal ulcers. H2RAs and PPIs were effective for the prevention of L-ASA-induced gastroduodenal ulcers. The cessation of L-ASA before endoscopy might lead to the underestimation of L-ASA-induced gastroduodenal injury.

Key words: low-dose aspirin (L-ASA), gastroduodenal ulcers, risk factors, preventive factors, cessation

(Intern Med 49: 2537-2545, 2010)

(DOI: 10.2169/internalmedicine.49.3824)

Introduction

Low-dose aspirin (L-ASA), commonly defined as 75-325 mg daily, is used for secondary prevention of ischemic heart disease and ischemic cerebrovascular disease. There are many reports of scientific evidence of the efficiency of L-ASA (1-5). In Japan, since 2000, treatment with L-ASA has

been permitted as a medical service under health insurance for the prevention of thrombus and embolus in patients suffering from ischemic heart disease or ischemic cerebrovascular disease.

The tendency for L-ASA to be prescribed has increased, because the number of patients with advanced age, diabetes and hypertension, which are risk factors for ischemic heart disease, is increasing (6).

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Received for publication April 16, 2010; Accepted for publication August 18, 2010

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On the other hand, it is well known that L-ASA induces gastroduodenal mucosal injury as an adverse effect similar to other non-steroidal anti-inflammatory drugs (NSAIDs). Because the number of L-ASA prescriptions is high, the absolute number of gastroduodenal mucosal injuries should not be ignored even if the frequency of mucosal injury is small. L-ASA is usually needed for a long time, and sometimes other anti-platelet drugs and anticoagulants are co-prescribed, leading to an increased risk of L-ASA-induced mucosal injury that may develop as a sudden bleeding peptic ulcer without pain, and it may be fatal.

In Japanese patients, Nakayama et al reported that the prevalence of L-ASA related bleeding peptic ulcers was steadily increasing in association with the increasing prescription of L-ASA for cardiovascular disease and cerebrovascular disease (7). The ACCF/ACG/AHA Expert Consensus in 2008 reported that the use of L-ASA (75-325 mg per day) was associated with a 2- to 4-fold increase of the risk for upper gastrointestinal (GI) events (8). A recent Japanese multicenter case-control study consisting of 175 patients hospitalized with upper GI bleeding and 347 controls identified from population registries in the same district by telephone interviews reported that the odds ratio of upper GI bleeding among L-ASA users was 7.7 (9).

Although there are few studies on the risk factors for gastroduodenal mucosal injury in patients receiving L-ASA, similar factors identified for other NSAIDs-induced gastroduodenal mucosal injury have been suggested as risk factors for L-ASA-induced gastroduodenal mucosal injury. These factors include a high aspirin dose, history of peptic ulcer or ulcer complication, use of NSAIDs, advanced age, concurrent use of anticoagulants, and the presence of severe disease (10). Some reports have pointed out that concurrent use of antiplatelet drugs is a risk factor (11-13). In Japanese patients, however, the risk factors for L-ASA-induced gastroduodenal mucosal injury have not been fully investigated.

In this retrospective study, we aimed to elucidate the risk factors and preventive factors associated with L-ASA-induced gastroduodenal mucosal injury in Japanese patients receiving L-ASA for arteriosclerotic disease.

Methods

Patients

This was a retrospective observational study performed at Kobe University Hospital from December 2005 through November 2006, and Miki City Hospital from January through December 2007 among patients receiving L-ASA for arteriosclerotic disease.

To select L-ASA users, we chose outpatients in the Department of Cardiovascular Disease of Internal Medicine receiving L-ASA during the investigation period, using the medical treatment fee database of each hospital. Among them, patients with cardiovascular disease or cerebrovascular disease, who had been receiving L-ASA regularly for more

than one month and had undergone endoscopy, were enrolled in this study as L-ASA users.

We examined the medical records of L-ASA users, and investigated patients' clinical characteristics, including sex, age, underlying disease, peptic ulcer history, concomitant drugs [i.e. gastric agents, anticoagulants (warfarin potassium), antiplatelet drugs (ticlopidine HCl, clopidogrel sulfate), NSAIDs, corticosteroids], the presence of *Helicobacter pylori* (HP) infection, reason for endoscopy [abdominal symptoms (i.e. reflux symptoms, abdominal pain, indigestion, obvious bleeding signs (hematemesis, tarry stool) or occult bleeding signs (anemia, fecal occult blood positive))], interruption of L-ASA before endoscopic examination, and endoscopic findings. A peptic ulcer history was confirmed by inclusion in the medical records and/or endoscopic findings of gastroduodenal mucosal scars. Drugs that were prescribed regularly during the L-ASA treatment period, including the day of endoscopic examination, were defined as concomitant drugs. Newly prescribed drugs within one week before endoscopic examination were not considered as concomitant drugs, although one patient had been prescribed proton pump inhibitor (PPI) 1 day before endoscopy and was classified into the no gastric agents group (None). According to the concomitant prescription of gastric agents, the patients were divided into five groups: PPI user, histamine type 2-receptor antagonist (H2RA) user, prostaglandin analogue (PA) user, cytoprotective gastric agents (C) user, and None. Patients receiving any cytoprotective gastric agents and co-prescribed PPI, H2RA, or PA were classified as PPI, H2RA, or PA users, respectively. One patient co-prescribed PPI and PA was classified as a PPI user.

HP status was determined by the presence of serum HP IgG antibodies, urea breath test (UBT), or culture using gastric mucosal specimens obtained during an endoscopic examination. It was based on a description in the medical records that the reason for endoscopy was anemia, and was not defined by the hemoglobin value. The doctor in charge of the patient decided whether the cessation of L-ASA would be possible before endoscopy, after taking the patient's underlying disease into consideration. The cessation period of L-ASA before endoscopic examination was 7 days in almost all patients, although one patient had 3-day cessation and one patient had 5-day cessation.

Patients who were considered to have unstable underlying diseases were excluded from this study because their unstable general state might have affected their gastroduodenal mucosa. The exclusion criteria were as follows; patients with unstable ischemic heart disease or with ischemic heart disease after stenting treatment or open-heart surgery (i.e. coronary artery bypass graft) for six months, patients with unstable cerebrovascular disease or within three months after an episode, patients with malignancy within five years after the diagnosis of malignancy, patients after upper gastrointestinal tract, biliary tract or pancreatic disease surgery, patients within one month after any surgery, and patients with serious injury to the liver, kidney or lung. We collected and ex-

Table 1. Patient Background (n=400)

		total	
Sex (male : female)		250 : 150	
Age (years)	mean	71	
	(range)	(24–92)	
Hospital (Kobe : Miki)		182 : 218	
		n	(%)
Causative disease with L-ASA			
ischemic heart disease		235	(59%)
cerebrovascular disease		96	(24%)
arteriosclerosis obliterans		32	(8.0%)
diabetes mellitus		24	(6.0%)
collagen disease		13	(3.0%)
Peptic ulcer history		40	(10%)
<i>Helicobacter pylori</i> infection			
(+)		47	(12%)
(+)		29	(7.3%)
(-)		18	(4.5%)
unknown		353	(88%)
Reason for endoscopy			
abdominal symptom		186	(47%)
reflux symptom		46	(12%)
abdominal pain		58	(15%)
indigestion		13	(3.3%)
obvious bleeding sign		24	(6.0%)
occult bleeding sign		45	(11%)
screening		214	(53%)
L-ASA before endoscopy			
non-cessation		183	(46%)
cessation		217	(54%)
Abbreviations:			
L-ASA: low-dose aspirin			

amined patient data according to the ethics rules of each institution.

Endoscopic findings

All endoscopic examinations were recorded digitally. The extent of gastroduodenal mucosal injury was expressed in terms of Kobayashi-Mizushima's modified Lanza score (MLS); numerically from zero (no injury) to five (ulcer) for gastric injury or four (ulcer) for duodenal injury (14–17). We defined an ulcer as a mucosal deficit of more than 3 mm in diameter. The endoscopic findings were evaluated by one experienced endoscopist (I.T.) in a blind manner after collecting all patient data.

Statistical analysis

To evaluate differences in the prevalence of injury, we used the χ^2 test or Fisher's exact probability test. To identify the factors associated with gastroduodenal ulcers, multiple

logistic regression analysis was performed and the odds ratio (OR) and 95% confidence interval (CI) were obtained. We compared the MLS using the Mann-Whitney test. All analyses were performed using the STATA/SE statistical software system version 10 (StataCorp., College Station, TX, USA). $p < 0.05$ was defined as significant.

Results

Patient characteristics

During the investigation period, cardiologists at each hospital prescribed L-ASA (enteric-coated or buffered) to 3,311 patients (1,341 patients at Kobe University Hospital and 1,970 patients at Miki City Hospital). Upper gastrointestinal endoscopy was performed in 957 of the 3,311 patients (29%). After selection according to inclusion and exclusion criteria, 400 patients (12%) were finally enrolled in this study.

Patient background is shown in Table 1, 2. Of 400 patients, 250 (62%) were men (mean age, 70 years old) and 150 (38%) were women (mean age, 72 years old). As the causative disease of L-ASA use, ischemic heart disease was present in 235 patients (59%), cerebrovascular disease in 96 patients (24%), arteriosclerosis obliterans (ASO) in 32 patients (8.0%), diabetes mellitus (DM) in 24 patients (6.0%), and collagen disease in 13 patients (3.0%).

Forty patients (10%) had a past history of peptic ulcer. In 35 patients (88%), peptic ulcer history was confirmed by both a description in the medical records and the endoscopic findings of gastroduodenal mucosal scars. In 5 patients, a peptic ulcer history (2 gastric ulcers and 3 duodenal ulcers) was confirmed by inclusion in the medical records only.

In 128 patients (32%), no gastric agents were co-prescribed, while co-prescription of cytoprotective gastric agents, PA, H2RAs and PPIs, was observed in 67 (17%) (i. e. Teprenone in 40 (10%), Rebamipide in 15 (3.9%), Sucralfate hydrate in 5 (1.3%), and others in 7 (1.8%)), one (0.25%), 124 (31%) [i.e. quarter-dose H2RAs in 7 (1.7%), half-dose H2RAs in 63 (15.8%), and full-dose H2RAs in 54 (13.5%)], and 80 (20%) [i.e. half-dose PPIs in 34 (8.5%), and full-dose PPIs in 46 (11.5%)] patients, respectively. Twenty-eight patients received PPI and cytoprotective gastric agents, and 35 patients received H2RA and cytoprotective gastric agents simultaneously. Co-prescription of anti-coagulants, anti-platelets, NSAIDs, and corticosteroids was observed in 46 (12%), 41 (10%), 29 (7.3%), and 36 (9.0%) patients, respectively. HP infections were investigated in 47 patients (12%), 29 of which (62%) were found to be HP positive. Five of 18 HP-negative patients had a history of HP eradication therapy.

Regarding the reason for endoscopy, 186 patients (47%) had abdominal symptoms; reflux symptoms, abdominal pain, indigestion, obvious bleeding signs, and occult bleeding signs were observed in 46 (12%), 58 (15%), 13 (3.3%), 24 (6.0%), and 45 (11%) patients, respectively. Of 45 patients

Table 2. Concomitant Drugs (n=400)

	total	
	n	(%)
Gastric agents		
None	128	(32%)
Cytoprotective gastric agent	67	(17%)
PA	1	(0.25%)
H2RA	124	(31%)
quarter-dose H2RA	7	(1.7%)
half-dose H2RA	63	(15.8%)
full-dose H2RA	54	(13.5%)
PPI	80	(20%)
half-dose PPI	34	(8.5%)
full-dose PPI	46	(11.5%)
Other Concomitant drugs		
anticoagulant	46	(12%)
warfarin		
antiplatelet drug	41	(10%)
ticlopidine	37	(9.3%)
clopidogrel	4	(1.0%)
NSAIDs	29	(7.3%)
non-selective	25	(6.3%)
selective inhibitor of COX-2	4	(1.0%)
Corticosteroid	36	(9.0%)

Abbreviations:

L-ASA: low-dose aspirin, C: Cytoprotective gastric agents

H2RA: histamine type 2-receptor antagonists, PPI: proton pump inhibitors

PA: prostaglandin analogues, NSAIDs: non-steroidal anti-inflammatory drugs

COX: cyclo-oxygenase

with occult bleeding signs, the mean hemoglobin level of 35 patients who underwent endoscopy for the examination of anemia was 9.9 mg/dL (4.4-15.8). Two hundred fourteen patients (53%) underwent endoscopy for screening. Before the endoscopic examination, L-ASA administration was interrupted in 217 patients (54%) to decrease the risk of endoscopy complications, such as bleeding after biopsy.

Prevalence of gastroduodenal mucosal injury

The MLS for gastric mucosal lesions was 0 in 157 (39%), 1 in 95 (24%), 2 in 36 (9.0%), 3 in 28 (7.0%), 4 in 52 (13%), and 5 in 32 (8.0%), and the MLS for duodenal mucosal lesions was 0 in 365 (91%), 1 in 14 (3.5%), 2 in 7 (1.8%), 3 in 2 (0.50%), and 4 in 12 (3.0%).

Of 400 patients, 243 (61%), 35 (8.8%), and 249 (62%) had gastric mucosal lesions, duodenal mucosal lesions, and gastroduodenal mucosal lesions (MLS ≥ 1), respectively. Thirty-two (8.0%), 12 (3.0%), and 41 (10%) patients had gastric ulcers (MLS=5), duodenal ulcers (MLS=4), and gastroduodenal ulcers, respectively. Gastric mucosal lesions (MLS ≥ 1) were significantly more frequently observed than duodenal mucosal lesions (MLS ≥ 1) (61% vs 8.8%; $p=0.005$). Gastric ulcers (MLS=5) were more frequently ob-

served than duodenal ulcers (MLS=4), but the difference was not statistically significant (8.0% vs 3.0%; $p=0.062$).

Bivariate analysis and multiple logistic regression analysis

To identify the factors associated with L-ASA-induced gastroduodenal ulcers, bivariate analysis using the χ^2 test or Fisher's exact probability test, and multiple logistic regression analysis were performed. The possible risk and preventive factors included sex, advanced age, peptic ulcer history, concomitant anticoagulants, concomitant antiplatelet drugs, concomitant NSAIDs, concomitant corticosteroids, presence of abdominal symptoms, concomitant gastric agents, and cessation of L-ASA before endoscopy.

In bivariate analysis, peptic ulcer history, the presence of abdominal symptoms, cytoprotective gastric agents, H2RA, and cessation of L-ASA were significantly associated with L-ASA-induced gastroduodenal ulcers. PPI was significantly associated with L-ASA-induced gastric ulcers. Patients with two or more of five factors [i.e. advanced age (≥ 75), concomitant anticoagulants, concomitant antiplatelet drugs, concomitant NSAIDs, and concomitant corticosteroids] had a significantly higher frequency of L-ASA-induced gastroduo-

Table 3. Bivariate Analysis of the Factors Associated with Gastroduodenal Ulcers in Patients Receiving L-ASA

			G		D		G∨D	
factors		n / n	% / %	p-value	% / %	p-value	% / %	p-value
Sex	male / female	250 / 150	7.6% / 8.7%	0.70	4.0% / 1.3%	0.22	11% / 9.3%	0.64
Advanced age	(70yr)	70≤ / <70	245 / 155	8.2% / 7.7%	0.88	3.3% / 2.6%	0.77	11% / 9.7%
	(75yr)	75≤ / <75	165 / 235	9.1% / 7.2%	0.50	3.6% / 2.6%	0.53	12% / 8.9%
	(80yr)	80≤ / <80	70/330	8.6%/7.9%	0.85	4.3%/2.7%	0.45	11.%/10%
								0.72
Peptic ulcer history	(+) / (-)	40 / 360	15% / 7.2%	0.085	10% / 2.2%	0.024*	23% / 8.9%	0.007**
C	(+) / (-)	67 / 333	15% / 6.6%	0.022*	3.0% / 3.0%	1.00	18% / 8.7%	0.023*
H2RA	(+) / (-)	124 / 276	3.2% / 10%	0.017*	1.6% / 3.6%	0.36	4.8% / 13%	0.017*
PPI	(+) / (-)	80 / 320	2.5% / 9.4%	0.040*	2.5% / 3.1%	1.00	5.0% / 12%	0.099
Anticoagulant	(+) / (-)	46 / 354	11% / 7.6%	0.40	2.2% / 3.1%	1.00	13% / 9.9%	0.51
Antiplatelets	(+) / (-)	41 / 359	12% / 7.5%	0.36	2.4% / 3.1%	1.00	15% / 9.7%	0.33
NSAIDs	(+) / (-)	29 / 371	17% / 7.3%	0.070	3.4% / 3.0%	0.60	21% / 9.4%	0.054
Corticosteroids	(+) / (-)	36 / 364	8.3% / 8.0%	1.00	0.0% / 3.3%	0.61	8.3% / 10%	1.00
Reason for endoscopy	abdominal symptom (+) / (-)	186 / 214	11% / 5.1%	0.024*	5.4% / 0.93%	0.015*	16% / 5.6%	0.001**
L-ASA	cessation / non-cessation	217 / 183	1.8% / 15%	<0.001***	0.92% / 5.4%	0.015*	2.7% / 19%	<0.001***
Summation of the factors	2≤ / <2	67 / 333	16% / 6.3%	0.005**	3.0% / 3.0%	1.00	19% / 8.4%	0.007**

Abbreviations:

L-ASA: low-dose aspirin, C: Cytoprotective gastric agents

H2RA: histamine type 2-receptor antagonists, PPI: proton pump inhibitors

NSAIDs: non-steroidal anti-inflammatory drugs

G: gastric ulcer, D: duodenal ulcer, GVD: gastric or duodenal ulcer

*p<0.05, **p<0.01, ***p<0.001

denal ulcers than patients with one or fewer of the five factors (Table 3).

In multiple logistic regression analysis, a peptic ulcer history, presence of abdominal symptoms, H2RA, PPI, and cessation of L-ASA were significantly associated with L-ASA-induced gastroduodenal ulcers; the OR (CI) were 5.49 (1.82-16.55), 4.56 (1.93-10.75), 0.13 (0.04-0.40), 0.12 (0.03-0.42) and 0.11 (0.04-0.29), respectively. Another multiple logistic regression analysis, with more than two of five factors, was assumed as one of the explanatory variables, patients with two or more of five factors [i.e. advanced age (≥ 75), concomitant anticoagulants, concomitant antiplatelet drugs, concomitant NSAIDs and concomitant corticosteroids] were significantly associated with L-ASA-induced gastroduodenal ulcers [OR (CI): 2.39 (1.002-5.69)] (Table 4).

Comparison between the L-ASA cessation group and the L-ASA non-cessation group

We compared the clinical characteristics between the L-ASA cessation group and the L-ASA non-cessation group. In the L-ASA cessation group, significantly more patients were enrolled in Miki City Hospital [182 (84%) in Miki City Hospital vs 35 (16%) in Kobe University Hospital; p<0.001]. Patients with a peptic ulcer history were significantly more frequently observed in the L-ASA non-cessation group than in the L-ASA cessation group [28 (15%) in non-cessation group vs 12 (5.5%) in cessation group; p=0.001].

Also, there was a significant difference in the reasons for endoscopy between the two groups. In the L-ASA cessation group, patients with obvious bleeding signs were significantly less frequently observed than in the L-ASA non-cessation group [3 (1.4%) in cessation group vs 21 (11%) in non-cessation group; p<0.001].

Table 5 shows the details of the MLS of gastric mucosal lesions in the L-ASA cessation and L-ASA non-cessation groups. The MLS for gastric mucosal lesions in the L-ASA cessation group was significantly smaller than in the L-ASA non-cessation group (1.28 vs 1.87; p=0.0068). In PPI and H2RA users, although the MLS for gastric mucosal lesions in the L-ASA cessation group was smaller than in the L-ASA non-cessation group, there was no statistical significance (0.84 vs 1.02; p=0.45 with PPI, 1.05 vs 1.39; p=0.38 with H2RA). In the L-ASA non-cessation group, the MLS of both PPI users and H2RA users for gastric mucosal lesions were significantly lower than in the no gastric agent group (1.02 vs 2.48; p=0.002 with PPI, 1.39 vs 2.48; p=0.012 with H2RA). There was no significant difference in the MLS between cytoprotective gastric agent users and the no gastric agent group (2.87 vs 2.48; p=1.00). In the L-ASA cessation group, although the MLS of both PPI users and H2RA users for gastric mucosal lesions were similarly lower than in the no gastric agent group, there was no statistical significance (0.84 vs 1.49; p=0.13 with PPI, 1.05 vs 1.49; p=0.50 with H2RA); however, the prevalence of gastric mucosal lesions

Table 4. Multivariate Analysis of the Factors Associated with Gastroduodenal Ulcers in Patients Receiving L-ASA

		G			D			GVD		
factors		OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Sex	male	0.63	(0.26-1.50)	0.29	3.01	(0.57-15.87)	0.19	0.96	(0.43-2.13)	0.91
Advanced age (75yr)	75≤	1.47	(0.64-3.38)	0.37	1.48	(0.41-5.35)	0.55	1.63	(0.76-3.51)	0.21
Peptic ulcer history	(+)	3.47	(1.01-11.98)	0.049*	11.46	(1.85-71.04)	0.009**	5.49	(1.82-16.55)	0.003**
C	(+)	0.88	(0.32-2.45)	0.81	0.62	(0.09-4.23)	0.63	0.92	(0.35-2.41)	0.86
H2RA	(+)	0.11	(0.03-0.39)	0.001**	0.18	(0.03-1.11)	0.065	0.13	(0.04-0.40)	<0.001***
PPI	(+)	0.07	(0.01-0.37)	0.002**	0.17	(0.02-1.41)	0.10	0.12	(0.03-0.42)	0.001**
Anticoagulant	(+)	1.26	(0.39-4.10)	0.70	0.63	(0.07-5.92)	0.69	1.22	(0.40-3.67)	0.73
Antiplatelets	(+)	1.53	(0.45-5.16)	0.49	0.60	(0.06-5.89)	0.66	1.32	(0.42-4.11)	0.64
NSAIDs	(+)	2.47	(0.62-9.91)	0.20	1.46	(0.12-17.83)	0.77	2.51	(0.68-9.32)	0.17
Corticosteroids	(+)	1.34	(0.26-7.01)	0.73	(-)	(-)	(-)	0.79	(0.16-3.88)	0.77
Reason for endoscopy	abdominal symptom	3.29	(1.32-8.23)	0.011*	10.30	(1.68-63.19)	0.012*	4.56	(1.93-10.75)	0.001**
L-ASA	cessation	0.09	(0.03-0.27)	<0.001***	0.23	(0.05-1.18)	0.078	0.11	(0.04-0.29)	<0.001***
Summation of the factors	2≤	2.71	(1.07-6.88)	0.036*	0.86	(0.17-4.49)	0.86	2.39	(1.002-5.69)	0.049*

Abbreviations:

L-ASA: low-dose aspirin, C: Cytoprotective gastric agents

H2RA: histamine type 2-receptor antagonists, PPI: proton pump inhibitors

NSAIDs: non-steroidal anti-inflammatory drugs

G: gastric ulcer, D: duodenal ulcer, GVD: gastric or duodenal ulcer

CI: confidence interval, OR: odds ratio

*p<0.05, **p<0.01, ***p<0.001

Table 5. Gastric Mucosal Injury Classified according to MLS in the L-ASA Cessation Group and the L-ASA Non-cessation Group (n=400)

L-ASA before endoscopy			MLS (stomach)						Mean scores
		total	0	1	2	3	4	5	
cessation	gastric agents	n=217(54%)	91(42%)	60(27%)	21(9.7%)	9(4.2%)	32(15%)	4(1.8%)	1.28***
	None	76(35%)	27(36%)	22(29%)	8(11%)	3(4.0%)	14(18%)	2(2.6%)	1.49
	C	36(17%)	11(31%)	10(28%)	3(8.3%)	2(5.6%)	9(25%)	1(2.8%)	1.75
	PA	0(0.0%)							n/a
	H2RA	62(28%)	26(42%)	20(32%)	8(13%)	3(4.8%)	5(8.1%)	0(0.0%)	1.05
	[quarter/half/full]	[1/33/28]	[1/12/13]	[0/12/8]	[0/4/4]	[0/1/2]	[0/4/1]	[0/0/0]	[0.00/1.18/0.93]
	PPI	43(20%)	27(63%)**	8(19%)	2(4.7%)	1(2.3%)	4(9.3%)	1(2.3%)	0.84
	[half/full]	[21/22]	[12/15]	[4/4]	[1/1]	[1/0]	[2/2]	[1/0]	[1.05/0.64]
non-cessation	gastric agents	n=183(46%)	66(36%)	35(19%)	15(8.2%)	19(10%)	20(11%)	28(15%)	1.87
	None	52(28%)	15(29%)	7(13%)	4(7.7%)	4(7.7%)	8(15%)	14(27%)	2.48
	C	31(17%)	6(19%)	2(6.5%)	4(13%)	6(19%)	4(13%)	9(29%)	2.87
	PA	1(0.55%)	1(100%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0.00
	H2RA	62(34%)	24(39%)	18(29%)	5(8.1%)	6(9.7%)	5(8.1%)	4(6.5%)**	1.39*
	[quarter/half/full]	[6/30/26]	[4/10/10]	[1/12/5]	[0/1/4]	[0/3/3]	[0/3/2]	[1/1/2]	[1.00/1.33/1.54]
	PPI	37(20%)	20(54%)*	8(22%)	2(5.4%)	3(8.1%)	3(8.1%)	1(2.7%)*	1.02**
	[half/full]	[13/24]	[11/9]	[1/7]	[1/1]	[0/3]	[0/3]	[0/1]	[0.23/1.46]

Abbreviations:

L-ASA: low-dose aspirin, C: Cytoprotective gastric agents

H2RA: histamine type 2-receptor antagonists, PPI: proton pump inhibitors

PA: prostaglandin analogues, n/a: not applicable

MLS: modified Lanza score, *p<0.05, **p<0.01 compared with None, ***p<0.01 compared with non-cessation

(MLS ≥ 1) in PPI users in the L-ASA cessation group was significantly lower than in patients receiving no prevention therapy (37% vs 64%; $p=0.004$).

Discussion

In this retrospective study, 62% of patients receiving L-ASA had gastroduodenal mucosal lesions (MLS ≥ 1), and 10% of patients had gastroduodenal ulcers. Niv et al reported in their prospective study that 48% of asymptomatic L-ASA users had gastroduodenal mucosal lesions (18). In Japanese patients, Nema et al reported that gastroduodenal mucosal lesions were found in 48.4% of patients with ischemic heart disease (19). Their reported prevalence rates of L-ASA-induced gastroduodenal mucosal lesions seem to be lower than in the present study. The difference in the prevalence rate might be due to differences in the candidate patients. In our study, about half of the L-ASA users had abdominal symptoms, including gastrointestinal bleeding signs. In this study, gastric mucosal lesions were significantly more observed than duodenal mucosal lesions (61% vs 8.8%; $p=0.005$) in L-ASA users, consistent with a previous report (18). Although the frequency of gastric mucosal lesions in L-ASA users is high, it seems that there is no need to treat patients with mucosal injury of MLS=1-3 without symptoms. Occasionally, treatment may be necessary in patients with mucosal injury of MLS=4 to prevent aggregation.

We focused on gastroduodenal ulcers requiring treatment, and evaluated the factors associated with L-ASA-induced gastroduodenal ulcers in this study. Multiple logistic regression analysis revealed that a peptic ulcer history and the presence of abdominal symptoms were significant risk factors for L-ASA-induced gastroduodenal ulcers. A history of peptic ulcer was previously reported to be associated with a higher risk of upper gastrointestinal bleeding in L-ASA users (20). In this study we were not able to confirm the endoscopic findings of peptic ulcer scars in five patients who were considered to have a past history of peptic ulcer from the medical records. We speculate that the gastroduodenal ulcer scars had become unclear after healing, but we could not reject the possibility of erroneous history taking.

In regard to abdominal symptoms, a poor correlation is reported between the presence of epigastric symptoms and gastroduodenal ulcers (21); however, the significant association observed in this study between the presence of abdominal symptoms and L-ASA-induced gastroduodenal ulcers might be expected because the enrolled L-ASA users included many symptomatic patients with obvious bleeding signs.

In this study, the possible risk factors for L-ASA-induced gastroduodenal lesions included factors [i.e. advanced age (22), concomitant anticoagulants (23), concomitant antiplatelet drugs (11-13), concomitant NSAIDs (24) and concomitant corticosteroids (25) that have been previously reported to be associated with L-ASA-induced gastrointestinal

complications. These five factors were not significantly associated with L-ASA-induced gastroduodenal ulcers in this study. Observational studies from Japan demonstrated that neither concomitant warfarin (12, 26) nor concomitant corticosteroids (26) was a significant risk factor for peptic ulcer in L-ASA users, which is consistent with our results. In this study, however, patients with two or more of these five factors were significantly associated with a higher prevalence of L-ASA-induced gastroduodenal ulcers, suggesting that summation of the risk factors is important for L-ASA-induced gastroduodenal ulcers.

As for concomitant NSAIDs, we speculated that NSAIDs were not regarded as significant risk factors in multiple regression analysis because of the small number of NSAID-co-prescribed L-ASA users in this study. In addition, 18 of 29 patients receiving NSAIDs were co-prescribed anti-ulcer drugs, which may have led to underestimation of the risk of NSAIDs. Multiple regression analysis in the subgroup with cytoprotective gastric agents or no gastric agents revealed that concomitant NSAIDs were a significant risk factor for gastroduodenal ulcers in L-ASA users [OR (CI): 5.47 (1.11-26.92); $p=0.037$].

Moreover, using multiple logistic regression analysis we identified the use of PPI, use of H2RA, and the cessation of L-ASA before endoscopy as preventive factors associated with L-ASA-induced gastroduodenal ulcers. A recent case-control study reported that both PPIs and H2RAs significantly reduced upper GI bleeding (27). In addition, the effectiveness of PPIs and H2RAs for the prevention of L-ASA-induced upper gastrointestinal mucosal injury was demonstrated in prospective randomized controlled trials (28, 29). In Japanese patients, the usefulness of PPIs and H2RAs was also reported in a previous observational study, case-control study and prospective cohort study (12, 30, 31), consistent with our study; however, a prospective randomized controlled study is necessary to clarify the effectiveness of PPIs and H2RAs for the prevention of L-ASA-induced gastroduodenal injury in Japanese patients. In multiple regression analysis, we were not able to find a significant preventive effect of cytoprotective gastric agents on L-ASA induced gastroduodenal mucosal lesions. In addition, although the MLS in PPI plus cytoprotective gastric agents users was smaller than the MLS in PPI users, no significant additional effect of cytoprotective gastric agents was observed (0.86 vs 0.96; $p=0.77$ in stomach, 0.14 vs 0.15; $p=0.69$ in duodenum).

L-ASA is often halted for three to seven days before endoscopy to decrease the risks associated with endoscopic procedures in Japanese patients. It is described in the Japanese guidelines for the diagnosis and treatment of gastric ulcer that cessation of NSAIDs is effective for NSAIDs-induced gastrointestinal injury (32); however, to our knowledge, no research has investigated whether L-ASA-induced gastroduodenal mucosal injury would improve with the short cessation of L-ASA, although it is reported that L-ASA induced gastroduodenal mucosal damage for a short period in

healthy volunteers (33). In this study, the cessation of L-ASA for seven days was significantly associated with the lower prevalence of L-ASA-induced gastroduodenal ulcers. These results support the Japanese guidelines for the diagnosis and treatment of gastric ulcer. On the other hand, these results suggest that the gastroduodenal mucosal injury induced by L-ASA might be underestimated in patients with the cessation of L-ASA before endoscopy. This underestimation of L-ASA-induced gastroduodenal mucosal injury is thought to be clinically important, because it may prevent the prescription of gastric agents which should be prescribed in high-risk L-ASA users. In particular, when L-ASA users with two or more risk factors stop L-ASA administration before endoscopy, the endoscopic findings should be interpreted carefully.

In this study, significant differences between the L-ASA cessation group and the L-ASA non-cessation group were observed in the hospital in which patients were enrolled, suggesting that the policy for the cessation of L-ASA differed according to the hospital. Also, there were significantly fewer patients with obvious bleeding signs in the L-ASA cessation group than in the L-ASA non-cessation group, suggesting that there was no time to discontinue L-ASA because urgent endoscopy was necessary.

There are limitations to interpreting the results in this study. There might be a selection bias in the patients enrolled in this study because the data were collected from L-ASA users who had undergone upper gastrointestinal endoscopy rather than from all L-ASA users. Many enrolled patients (47%) had abdominal symptoms. Moreover, the patients were registered from two hospitals and the disease severity of an underlying disease may have differed, although there was no difference in the rate of asymptomatic L-ASA users between the two hospitals. We are not able to deny the possibility that this bias affected the evaluation of risk factors for L-ASA-induced gastroduodenal mucosal lesions. Also, although medicine prescribed within one week before endoscopy was not considered a concomitant drug in this study, there was a difference in a prescription period of concomitant drugs by patients. This difference might have affected L-ASA-induced gastroduodenal mucosal lesions. As for concomitant PPI, there might be patients whose prescription period of concomitant PPI was not sufficient for healing gastroduodenal ulcers. And that might be the reason why PPI was not significantly associated with L-ASA-induced gastroduodenal ulcers in bivariate analysis. However, we were not able to evaluate the influence of the prescription period of a concomitant drug in this study. In addition, we did not evaluate *Helicobacter pylori* (HP) infection for L-ASA-induced gastroduodenal injury in this study because HP infection was investigated only in 47 patients (12%). Since one of 18 HP-negative patients determined by tissue culture had been receiving PPI, this patient's HP-negative result was possibly a false-negative. While there is a report that HP infection might be a risk factor of L-ASA-induced gastroduodenal injury (34), there is another report that it

might be a protective factor (35). The role of HP infection in L-ASA-induced gastrointestinal injury remains controversial. Also, we were not able to evaluate the extent to which the severity of an underlying disease influences L-ASA-induced gastroduodenal mucosal lesions because detailed data of the severity of an underlying disease were unknown in this study.

In summary, in this retrospective study, 10% of L-ASA users had gastroduodenal ulcers. A peptic ulcer history, the presence of abdominal symptoms and having two or more of five factors [i.e. advanced age (≥ 75), concomitant anti-coagulants, concomitant antiplatelet drugs, concomitant NSAIDs, and concomitant corticosteroids] were significant risk factors, and the use of PPI, use of H2RA, and the cessation of L-ASA before endoscopy were preventive factors for L-ASA-induced gastroduodenal ulcers. The cessation of L-ASA before endoscopy might lead to the underestimation of L-ASA-induced gastroduodenal injury.

Acknowledgement

This study was supported by a grant from the Global COE Program "Global Center of Excellence for Education and Research on Signal Transduction Medicine in the Coming Generation" from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (T.A.). We thank Dr. I. Kamae for helpful comments on statistical analysis.

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