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Prevalence and independent factors for gastroduodenal ulcers/erosions in asymptomatic patients taking low-dose aspirin and gastroprotective agents: the OITA-GF study

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Summary

Background: Although it is well known that aspirin causes gastroduodenal mucosal injury and that aspirin-induced gastroduodenal mucosal injury is often asymptomatic, the prevalence and independent factors for gastroduodenal mucosal injury have not been clarified in asymptomatic patients taking low-dose aspirin and gastroprotective agents.
Aim: To clarify the prevalence and independent factors for gastroduodenal ulcers/erosions in asymptomatic patients taking low-dose aspirin and gastroprotective agents.
Design: Prospective observational study.
Methods: We performed endoscopy in 150 asymptomatic patients taking low-dose aspirin and gastroprotective agents for at least 3 months.
Results: Gastroduodenal ulcers/erosions were observed in 37.3% [ulcers (4.0%); erosions (34.0%)]. Univariate logistic regression analyses showed that proton-pump inhibitor (PPI) use was negatively associated with gastroduodenal ulcers/erosions [odds ratio (OR) 0.35, 95% confidence interval (95% CI) 0.17–0.75, $P=0.007$]. A multivariate logistic regression analysis selected PPI use as the only independent factor for gastroduodenal ulcers/erosions (OR 0.35, 95% CI 0.14–0.86, $P=0.02$). None of the 53 patients with PPI use had any gastroduodenal ulcers, and 11 with standard-dose PPI use tended to have a lower prevalence of gastroduodenal erosions than 42 with low-dose PPI use (0% vs. 28.6%, $P=0.052$).
Conclusions: Gastroduodenal ulcers/erosions were observed in about one-third of asymptomatic patients taking low-dose aspirin and gastroprotective agents, and PPI use was a negative independent factor for gastroduodenal ulcers/erosions in those patients. In addition, standard-dose PPI therapy might be more effective in the prevention of aspirin-induced gastroduodenal mucosal injury than low-dose PPI therapy.

Introduction

Low-dose aspirin (75–325 mg/day) is widely used for primary and secondary prevention of cardiovascular events and prevention of coronary stent thrombosis.[1–5] The use of low-dose aspirin is associated with a 2- to 4-fold increased risk of upper gastrointestinal complications such as gastroduodenal ulcers and gastrointestinal bleeding.[6,7] There are only a few endoscopic studies investigating the exact prevalence of gastroduodenal mucosal injury in patients taking low-dose aspirin[8–10] (Table 1). Yeomans *et al.*[8] performed endoscopy in 187 patients taking low-dose aspirin and no gastroprotective agents and found gastroduodenal ulcers in 10.7% and gastroduodenal erosions in 63.1%.

Table 1 The prevalences of gastroduodenal ulcers/erosions in patients taking low-dose aspirin among previous studies and the present study

References	*n*	Mean age (years)	Male (%)	Upper gastrointestial symptoms	Definition of ulcers (size) (mm)	Gastroduodenal ulcers/erosions (%)	H_2 blockers (%)	PPIs (%)
Yeomans *et al.*[8]	187	49.9 (Edmonton) 61.0 (Melbourne) 63.9 (Nottingham) 61.3 (Sydney) 67.6 (Zaragoza)	64.2	+/–	≥3	Ulcers 10.7 Erosions 63.1	0	0
Niv *et al.*[10]	46	70	47.8	–	>3	47.8	10.9	13.0
Nema *et al.*[9]	190	69.7 (BA) 68.8 (ECA)	68.4	+/–	>5	48.4	30	4.7
The present study	150	71.6	68	–	≥3	37.3	36.7	35.3

BA: bufferin, ECA: Bayaspirin. The study by Yeomans *et al.* was performed at five centers. The study by Nema *et al.* consisted of 89 patients taking BA, 101 taking ECA and 46 controls not taking aspirin.

Nema *et al.*[9] performed endoscopy in 190 patients taking low-dose aspirin and found gastroduodenal ulcers/erosions in 48.4%. These studies included patients with and without upper gastrointestinal symptoms. Because it is well known that aspirin-induced gastroduodenal mucosal injury is often asymptomatic,[8,11] it would be expected that some of asymptomatic patients taking low-dose aspirin may have gastroduodenal erosions/ulcers. Niv *et al.*[10] investigated the prevalence of gastroduodenal ulcers/erosions in 46 asymptomatic patients taking low-dose aspirin and found gastroduodenal erosions/ulcers in 47.8%. In their study, only 24% of patients were taking a gastroprotective agent. Therefore, the prevalence and independent factors for gastroduodenal ulcers/erosions have not been clarified in asymptomatic patients taking low-dose aspirin and gastroprotective agents. In the present study, we examined these points.

Methods

The present study was conducted between January 2008 and December 2008 at three centers (Oita University Hospital, Oita Nakamura Hospital and Koseiren Tsurumi Hospital), in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the ethics committee at Oita University Hospital, and written informed consents were obtained from all patients before enrollment.

Patients

Eligible patients who were hospitalized to cardiology department of the three hospitals or attending cardiology outpatient clinics of these hospitals and who were taking low-dose aspirin and gastroprotective agents for the preceding ≥3 months were registered in this study. Inclusion criteria were as follows: age >20 years; no upper gastrointestinal symptoms (epigastric pain, burning or discomfort, heartburn, pain, acid regurgitation, nausea and bloating); no changes of gastroprotective agents within the preceding 3 months; no history of operations for the esophagus, stomach and duodenum; neither acute coronary syndrome nor stroke within the preceding 3 months; severe chronic heart failure (New York Heart Association functional Class IV); and no malignant diseases. Finally, 150 patients (102 men and 48 women, mean age of 71.6±10.0 years) were enrolled in this study and underwent esophagogastroduodenal endoscopy.

Demographic data

The following demographic data were collected: age, gender, body mass index, coronary risk factors, alcohol consumption, histories of cardiovascular disease, peptic ulcers and eradication of *Helicobacter pylori*, and current medications. Patients who reported that they drank alcohol everyday were considered as regular alcohol drinkers. Standard-dose proton-pump inhibitors (PPIs) were defined as lansoprazole of 30 mg/day, omeprazole of 20 mg/day and raveprazole of 20 mg/day, and low-dose PPIs were defined as lansoprazole of 15 mg/day, omeprazole of 10 mg/day and raveprazole of 10 mg/day.

Helicobacter pylori infection status

Helicobacter pylori infection was examined using a urine-based enzyme-linked immunosorbent assay (Otsuka Pharmaceutical, Tokyo, Japan).

The sensitivity, specificity and accuracy of this assay has been shown to be almost equivalent to serum-based enzyme-linked immunosorbent assays for identifying patients with *H. pylori* infection.[12,13]

Endoscopic examinations

Esophagogastroduodenal endoscopy was performed without cessation of aspirin because cessation of aspirin may affect gastroduodenal mucosal status. An ulcer was defines as a mucosal defect having significant depth, measuring at least 3 mm over its longest diameter. An erosion was defined as a mucosal defect <3 mm. The evaluation was performed by experienced endoscopists who were blinded to all clinical data.

Statistical analysis

Continuous data are expressed as mean ± SD or median (first–third quartiles), and categorical data are expressed as *n* (%). Univariate and multivariate logistic regression analyses were performed to determine factors for gastroduodenal ulcers/erosions. A multivariate logistic regression analysis was performed using explanatory variables that showed $P<0.3$ in univariate logistic regression analyses. A *P*-value <0.05 was considered to be statistically significant. All analyses were performed using SS 12.0J for Windows (SPSS Inc, Tokyo, Japan).

Results

Patient characteristics are shown in Table 2. The doses of aspirin were 81 mg/day in five patients (3.3%), 100 mg/day in 143 patients (95.3%) and 200 mg/day in two patients (1.3%). The enteric coated and buffered formulations were being taken in 145 patients (96.7%) and five patients (3.3%), respectively. PPIs [lansoprazole ($n=31$), omeprazole ($n=15$) and rabeprazole ($n=7$)], H_2 blockers [famotidine ($n=37$), ranitidine ($n=14$) and nizatidine ($n=4$)] and mucoprotective agents [rebamipide ($n=15$), cetraxate ($n=14$), teprenone ($n=12$), azulenesulfonate ($n=6$), plaunotol ($n=2$), isoglandin ($n=2$), ecebet ($n=1$) and sofalcone ($n=1$)] were being taken in 53 patients (35.3%), 55 patients (36.7%) and 53 patients (35.3%), respectively.

Gastroduodenal ulcers/erosions were observed in 56 patients (37.3%): ulcers in six (4.0%); erosions in 51 (34.0%) (Figure 1). One patient had a gastric ulcer and gastric erosions. Table 3 shows detailed data of six patients with a gastric or duodenal ulcer. Three of six patients with a gastric or duodenal ulcer had a positive *H. pylori* urinary test.

Table 2 Patient characteristics

Age (years)	71.6 ± 10.0
Male	102 (68.0)
Body mass index (kg/m^2)	24.0 ± 3.3
Hypertension	125 (83.3)
Diabetes mellitus	56 (37.3)
Current smoker	16 (10.7)
Regular alcohol drinker	51 (34.0)
Coronary heart disease	128 (85.3)
Stroke	14 (9.3)
PCI	113 (75.3)
Atrial fibrillation	27 (18.0)
History of peptic ulcer	45 (30.0)
History of eradication of *H. pylori*	10 (6.7)
Positive urinary *H. pylori* antibody	68 (45.3)
Dose of aspirin	
81 mg/day	5 (3.3)
100 mg/day	143 (95.3)
200 mg/day	2 (1.3)
Type of aspirin	
Enteric-coated formulation	145 (96.7)
Buffered formulation	5 (3.3)
PPIs	53 (35.3)
H_2 blockers	55 (36.7)
Mucoprotective agents	53 (35.3)
Warfarin	37 (24.7)
NSAIDs	8 (5.3)
Steroids	0 (0)
Nitrates	71 (47.3)
Calcium antagonists	86 (57.3)
ACEIs	24 (16.0)
ARBs	84 (56.0)

Data are presented as mean ± SD or number (%). PCI: percutaneous coronary intervention; PPI: proton-pump inhibitor; NSAID: nonsteroidal anti-inflammatory drug; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker. Another abbreviation is as Table 1.

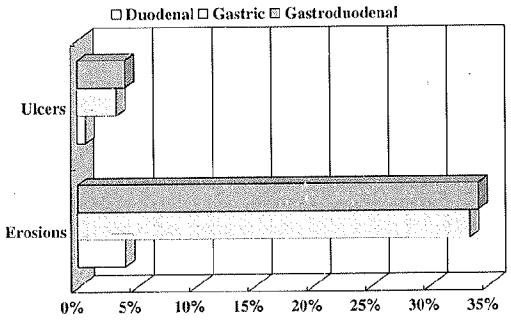

Figure 1. The prevalence of gastroduodenal ulcers/erosions.

Table 4 shows results of univariate and multivariate logistic regression analyses to determine factors for gastroduodenal ulcers/erosions. Univariate logistic regression analyses showed that PPI use was

Table 3 Detailed data of patients with a gastric or duodenal ulcer

Age (years)	Sex	Location	History of ulcers	Urinary *H. pylori* antibody	Gastroprotective agent
85	Male	Stomach	Gastric ulcer	–	Ranitidine
71	Female	Stomach	–	–	Cetraxate
71	Female	Stomach	Duodenal ulcer	+	Isogladine
84	Female	Stomach	–	+	Rebamipide
83	Male	Stomach	–	–	Nizatidine
71	Male	Duodenum	–	+	Rebamipide

Table 4 Univariate and multivariate logistic regression analyses to determine variables for gastroduodenal ulcers/erosions

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	0.99 (0.96–1.02)	0.58		
Male	0.89 (0.43–1.81)	0.89		
Hypertension	0.72 (0.30–1.71)	0.45		
Diabetes mellitus	0.79 (0.40–1.58)	0.51		
Current smoker	0.74 (0.24–2.25)	0.60		
Regular alcohol drinker	1.01 (0.50–2.05)	0.98		
Positive urinary *H. pylori* antibody	0.85 (0.44–1.66)	0.85		
History of eradication of *H. pylori*	0.40 (0.08–1.95)	0.26	0.42 (0.08–2.24)	0.31
History of peptic ulcer	0.78 (0.38–1.63)	0.78		
PPIs	0.35 (0.17–0.75)	0.007	0.35 (0.14–0.86)	0.02
H_2 blockers	1.52 (0.77–3.01)	0.23	0.83 (0.36–1.90)	0.66
Mucoprotective agents	1.32 (0.66–2.62)	0.44		
Warfarin	1.61 (0.76–3.43)	0.21	1.47 (0.65–3.32)	0.36
NSAIDs	1.73 (0.42–7.21)	0.45		
Calcium antagonists	0.62 (0.32–1.21)	0.16	0.73 (0.36–1.50)	0.39
Nitrates	0.72 (0.34–1.30)	0.24	0.71 (0.35–1.45)	0.34

Other abbreviations are as Tables 1 and 2.
OR: odds ratio, CI: confidence interval.

significantly associated with gastroduodenal ulcers/erosions [odds ratio (OR) 0.35, 95% confidence interval (95% CI) 0.17–0.75, $P=0.007$]. The following explanatory variables were entered into a multivariate logistic regression analysis: a history of eradication of *H. pylori*, PPI use, H_2 blocker use, warfarin use, calcium antagonist use and nitrate use. The multivariate logistic regression analysis showed that PPI use was the only independent factor for gastroduodenal ulcers/erosions (OR 0.35, 95% CI 0.14–0.86, $P=0.02$).

None of 53 patients with PPI use had any gastroduodenal ulcers. Figure 2 shows the prevalence of gastroduodenal erosions in 11 patients with standard-dose PPI use (lansoprazole of 30 mg/day in seven patients, omeprazole of 20 mg/day in three patients and raveprazole of 20 mg/day in one patient) and 42 patients with low-dose PPI use (lansoprazole of 15 mg/day in 24 patients, omeprazole of 10 mg/day in 12 patients and raveprazole of 10 mg/day in six patients). The former tended to have a lower prevalence of gastroduodenal erosions than the latter (0% vs. 28.6%, $P=0.052$).

Discussion

The major findings of the present study are as follows: (i) gastroduodenal ulcers/erosions were observed in 37.3% [ulcers (4.0%); erosions (34.0%)] of 150 asymptomatic patients taking low-dose aspirin and gastroprotective agents; (ii) PPI use was the only independent factor for gastroduodenal ulcers/erosions; (iii) none of patients with PPI use had any gastroduodenal ulcers; and (iv) patients with standard-dose PPI use tended to

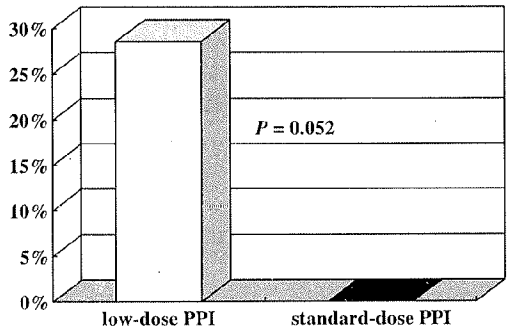

Figure 2. Comparisons of the prevalence of gastroduodenal erosions between patients with low-dose PPI use and those with standard-dose PPI use.

have a lower prevalence of gastroduodenal erosions than those with low-dose PPI use.

Low-dose aspirin causes gastrointestinal mucosal injury through topical injury to the mucosa and systemic effects by prostaglandin depletion.[14,15] Aspirin is non-ionized by the acid environment of the stomach and accumulates in gastric mucosal cells. Then, it alters the permeability of the cell membrane due to iron trapping and back-diffuses H^+ irons from the gastrointestinal lumen, leading to cellular toxicity. Inhibition of cyclo-oxygenase-1 pathway decreases production of prostaglandins that have protective effects on the stomach through the following mechanisms: an increase in mucosal blood flow, stimulation of the synthesis and secretion of mucus and bicarbonate, and promotion of epithelial proliferation. Depletion of prostaglandins makes a gastric environment more susceptible to topical attacks by endogenous factors including acid, pepsin and bile salts. In addition, low-dose aspirin promotes gastrointestinal bleeding through its antiplatelet effect.

It is well known that aspirin-induced gastroduodenal mucosal injury is often asymptomatic[8,11] because of an aspirin induced increase in a sensory threshold.[11] Niv *et al.*[10] investigated the prevalence of gastroduodenal ulcers/erosions in 46 asymptomatic patients taking low-dose aspirin and found these lesions in 47.8%. In their study, only 24% of patients were taking a gastroprotective agent. Therefore, the prevalence and independent factor for gastroduodenal ulcers/erosions have not been clarified in asymptomatic patients taking low-dose aspirin and gastroprotective agents. In addition, no information is available on the prevalence of gastroduodenal ulcers/erosions in asymptomatic patients taking low-dose aspirin and a PPI, which has been shown to be effective in the prevention of aspirin-induced gastroduodenal ulcers.[18] Therefore, it would be clinically important to examine these points. In the present study, gastroduodenal ulcers/erosions were observed in 37.3% of 150 asymptomatic patients taking low-dose aspirin and gastroprotective agents. The prevalence of gastroduodenal ulcers/erosions was relatively lower in the present study compared to the prevalences in previous studies.[8–10] This is thought to be because the present study consisted of asymptomatic patients taking gastroprotective agents together with low-dose aspirin. In the present study, none of 53 patients with PPI use had any gastroduodenal ulcers, and PPI use was the only negative independent factor for gastroduodenal ulcers/erosions, suggesting an efficacy of PPIs in the prevention of aspirin-induced gastroduodenal ulcers/erosions. It has been already shown that PPI therapy prevents upper gastrointestinal bleeding[16,17] and gastroduodenal ulcers[18] in patients taking low-dose aspirin. Because gastric acid more easily injures gastroduodenal mucosae under the environment of prostaglandin depletion, it would be expected that PPI therapy can protect aspirin-induced gastroduodenal mucosal injury through its strongly suppressive effect on gastric acid. Of interest, in the present study, patients with standard-dose PPI use had no gastroduodenal erosions and tended to have a lower prevalence of gastroduodenal erosions than those with low-dose PPI use. These suggest that standard-dose PPI therapy may be more effective in the prevention of aspirin-induced gastroduodenal mucosal injury than low-dose PPI therapy. No information is so far available with regard to the association between the dose of PPIs and the preventive effects on aspirin-induced gastroduodenal mucosal injury. Future studies are required to clarify whether standard-dose PPI therapy is more effective in the prevention of aspirin-induced gastroduodenal mucosal injury than low-dose PPI therapy.

In the present study, H_2 blocker use was not a negative independent factor for gastroduodenal ulcers/erosions. This might be because the majority (89%) of patients with H_2 blocker use was taking a low-dose H_2 blocker (famotidine of $\leq$20 mg/day, ranitidine of $\leq$150 mg/day or nizatidine of $\leq$150 mg/day). It was recently demonstrated that standard-dose famotidine (40 mg/day) is effective in the prevention of gastroduodenal ulcers in patients taking low-dose aspirin.[20] The association between the dose of H_2 blockers and aspirin-induced gastroduodenal mucosal injury remains to be further investigated.

The present study has a few limitations. First, we did not evaluate the exact administration duration and compliance of gastroprotective agents, which would affect gastroduodenal mucosal status. Second, the prevalences of PPI use and H_2 blocker

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