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BRIEF ARTICLE

Gender differences of low-dose aspirin-associated gastroduodenal ulcer in Japanese patients

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Abstract

AIM: To clarify the gender differences about the clinical features and risk factors of low-dose aspirin (LDA) (81-100 mg daily)-associated peptic ulcer in Japanese patients.

METHODS: There were 453 patients under treatment with LDA (298 males, 155 females) who underwent esophagogastroduodenoscopy at the Department of Gastroenterology and Hepatology of Hiratsuka City Hospital between January 2003 and December 2007. They had kept taking the LDA or started treatment during the study period and kept taking LDA during the whole period of observation. Of these, 119 patients (87 males, 32 females) were diagnosed as having LDA-associated peptic ulcer. We examined the clinical factors associated with LDA-associated peptic ulcer in both sexes.

RESULTS: A history of peptic ulcer was found to be the risk factor for LDA-associated peptic ulcer common to both sexes. In female patients, age greater than 70 years (prevalence ORs 8.441, 95% CI: 1.797-33.649, P = 0.0069) was found to be another significant risk factor, and the time to diagnosis as having LDA-associated peptic ulcer by endoscopy was significantly shorter than that in the male patients (P = 0.0050).

CONCLUSION: We demonstrated gender differences about the clinical features and risk factors of LDA-associated peptic ulcer. Special attention should be paid to aged female patients taking LDA.

Key words: Low-dose aspirin; Gender; Peptic ulcer

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INTRODUCTION

Low-dose aspirin (LDA) is one of the main agents used for the prevention of thromboembolic vascular events, and has the advantages of both low cost and a prolonged duration of antiplatelet action[1]; however, it is associated with a doubling of the risk of gastrointestinal bleeding, even at doses as low as 75 mg daily[2,3]. The gender differences in the clinical manifestations of LDA-associated gastroduodenal mucosal injury have not been well studied. The aim of this study was to clarify the clinical features and risk factors of LDA-associated gastroduodenal mucosal injury in both sexes.

MATERIALS AND METHODS

Patients

There were 453 patients under treatment with LDA (298 males; median age, 71 years; age range, 43-93 years and 155 females; median age, 73 years; age range, 47-95 years) who underwent esophagogastroduodenoscopy (EGD) at the Department of Gastroenterology and Hepatology of Hiratsuka City Hospital between January 2003 and December 2007. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Hiratsuka City Hospital. The exclusion criteria were: patients who were taking LDA for less than 7 d, patients who had been previously diagnosed or treated for LDA-associated gastroduodenal mucosal injury in the past, patients with gastric or duodenal cancer, history of gastric or esophageal surgery and any current active cancer. Detailed information about the drug treatment and other risk factors were obtained from the medical records and also from interviews with the patients when they underwent medical examination. Concomitant use of anti-ulcer drugs (proton-pump inhibitors (PPIs), Histamine type 2 receptor antagonists (H2RAs), muco-protective agents, anticoagulants and/or antiplatelets and antithrombotic agents was defined as starting with LDA or taken for more than 4 wk before receiving endoscopy.

Endoscopic assessments

Endoscopic examinations were performed in each patient. Only ulcers with whitish exudate that were over 5 mm in size[4] and had perceptible depth were included in the determination of the ulcer, with ulcer scars being excluded.

Helicobacter pylori infection status

The patients diagnosed to have ulcer were checked for *Helicobacter pylori* (*H. pylori*) infection using the *H. pylori* serum antibody assay, urea breath test, rapid urease test and *H. pylori* culture of two biopsy specimens obtained from the gastric body and antrum. If one of the tests was positive, the patient was labeled as *H. pylori*-positive, and if more than two of the tests were negative, the patient was labeled as *H. pylori*-negative.

Table 1 Clinical characteristics of patients taking LDA enrolled in the present study

	Patients with ulcer (n = 119)	Patients without ulcer (n = 334)	P-value
Gender (male/female)	87/32	211/123	NS
Age (yr), median (range)	73.0 (47-92)	72.0 (45-95)	NS
Male (n = 298)	70.0 (47-92)	71.0 (43-93)	NS
Female (n = 155)	77.0 (54-92)	73.0 (47-95)	0.0338
Underlying disease (male/female)			
Ischemic heart disease	77 (61/16)	205 (131/74)	NS
Cerebral infarction	22 (10/12)	70 (39/31)	NS
Atrial fibrillation	16 (13/3)	43 (28/15)	NS
Others	4 (3/1)	16 (13/3)	NS
Symptoms (male/female)			
Melena, hematemesis	46 (29/17)	1 (0/1)	< 0.0001
GI symptoms	31 (21/10)	107 (72/35)	NS[1]
Anemia	17 (14/3)	40 (21/19)	0.0156
Body weight loss	1 (1/0)	7 (5/2)	0.0087
Appetite loss	1 (1/0)	8 (2/6)	0.0028
None (medical check)	18 (15/3)	146 (96/50)	0.0025
Others	5 (2/0)	25 (15/10)	> 0.9999
Helicobacter pylori	62.3% (43/69)	-	
Male	66.7% (30/45)	-	
Female	54.2% (13/24)	-	

[1]Forty-six patients presented with melena and/or hematemesis and bleeding source in the stomach or duodenum identified by endoscopy and were excluded from GI symptoms in this analysis. LDA: Low-dose aspirin; GI: Gastrointestinal; NS: Not significant.

Statistical analysis

Statistical evaluation was carried out using Fisher's exact test, t-test or Mann-Whitney U-test and these variables were also evaluated by multivariate logistic regression model using a Wald statistic forward stepwise selection. The level of significance was set at $P < 0.05$. Statistical analyses were performed with Stat View software (SAS Institute, Cary, NC).

RESULTS

The baseline characteristics of the study population

The 453 patients under treatment with LDA who underwent EGD were included in this investigation. The baseline characteristics of the study population are summarized in Table 1. One hundred and nineteen (26.3%, 87 males, 32 females) of the 453 patients receiving LDA were diagnosed as having LDA-associated peptic ulcer, consisting of 92 patients with LDA-associated gastric ulcer (71 males, 21 females), 20 patients with duodenal ulcer (14 males, 6 females) and 7 patients with gastric and duodenal ulcers (2 males, 5 females).

The age of female patients with ulcer was greater than that of without ulcer (P = 0.0338). The most common indication for LDA was secondary prevention of ischemic heart disease (62.3%, 282/453). There were no significant differences in the distribution of underlying diseases between patients with ulcer and without ulcer (P = 0.8380). There were no significant differences in the presence of the gastrointestinal (GI) symptoms, defined as abdominal pain, nausea, reflux symptoms and/or the indigestion

Table 2 Univariate analysis to identify factors predictive of LDA-associated gastroduodenal ulcer in male and female patients

Factor	Male patients (n = 299)			Female patients (n = 155)		
	Patients with ulcer (n = 87)	Patients without ulcer (n = 211)	P-value	Patients with ulcer (n = 32)	Patients without ulcer (n = 123)	P-value
PPIs	1	22	0.0038	0	18	0.0253
H2RAs	16	53	NS	5	38	NS
Muco-protective agents	18	40	NS	6	18	NS
Hypertension	62	150	NS	21	88	NS
Hyperlipidemia	36	96	NS	14	51	NS
History of peptic ulcer	18	19	0.0109	9	9	0.0030
Diabetes mellitus	29	63	NS	11	30	NS
Insulin therapy	4	12	NS	3	3	NS
Anticoagulants	29	87	NS	11	35	NS
NSAIDs	3	25	NS	3	10	NS
Age ⩾ 70 yr	45	123	NS	28	85	0.0443
Alcohol	28	63	NS	6	12	NS
Smoking	22	36	NS	1	8	NS

PPIs: Proton-pump inhibitors; H2RAs: Histamine type 2 receptor antagonists; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table 3 Age-stratified prevalence of LDA-associated peptic ulcer in males and females

Age (yr)	Patients with ulcer (n = 119) (M/F)	Patients without ulcer (n = 334) (M/F)
40-49	2/0	4/3
50-59	15/2	20/7
60-69	24/2	64/28
70-79	33/17	94/55
80-89	10/11	26/27
90-	2/1	3/3

Table 4 Duration of LDA administration until diagnosis as having LDA-associated peptic ulcer in 106 patients

Month	Male (n = 78)	Female (n = 28)
-1	3	3
1-11	15	6
12-23	6	6
24-35	10	5
36-47	11	4
48-59	5	0
60-71	5	2
72-	23	2
Mean (min-max)	42 (1-223)	25.5 (1-130)

syndrome, between the patients with ulcer and without ulcer (P = 0.0761). Forty-six patients presented with melena and/or hematemesis and bleeding source in the stomach or duodenum identified by endoscopy were excluded from GI symptoms in this analysis. Moreover, even in patients with peptic ulcer, about half were asymptomatic.

Univariate analyses to identify predicted factors of LDA-associated gastroduodenal ulcer in both sexes were shown in Table 2. A history of peptic ulcer was found to be the only significant risk factor common to both sexes (male, P = 0.0109, female P = 0.0030), and age greater than 70 years was another risk factor in female patients (P = 0.0443). As shown in Table 3, there were no significant differences in the prevalence of LDA-associated peptic ulcer among age brackets in either sex (male, P = 0.3137, female P = 0.3612).

H. pylori infection status

The *H. pylori* infection status was determined in 69 patients (58.0%, 69/119), but remained unknown in the remaining 50 patients who were therefore not included in the statistical analysis of this parameter. Of the 69 patients, 62.3% (43/69) were *H. pylori*-positive [gastric ulcer, 69.1% (38/55); duodenal ulcer, 25.0% (2/8); gastric and duodenal ulcer, 50.0% (3/6)] and 26 (37.7%) were *H. pylori*-negative. There were no significant differences in the *H. pylori* infection rate between both sexes [male: 66.7% (30/45), female: 54.2% (13/24)] (P = 0.4344). The *H. pylori* infection rate was significantly lower in patients with LDA-associated ulcer as compared with that in patients with non-LDA-associated ulcer [including other nonsteroidal anti-inflammatory drugs (NSAIDs) associated ulcer] (77.0%, 419/544) diagnosed in the same study period (data are not shown in Tables) (P = 0.0112).

Time to diagnosis as having LDA-associated peptic ulcer by endoscopy

As shown in Table 4, we investigated the time from the start of LDA administration to the diagnosis as having LDA-associated peptic ulcer by endoscopy in 106 of the 119 patients (89.1%). LDA-associated peptic ulcer was diagnosed within the first month in 6 cases (5.7%) within the first 12 mo in 28 cases (26.4%), and within 5 years in 74 cases (69.8%). In female patients, the duration was significantly shorter than in male patients (P = 0.0050) (male: mean 42.0 mo; range, 1-223 mo, female: mean, 25.5 mo; range, 1-130 mo). The incidence of LDA-associated peptic ulcer seemed almost constant and did not decrease with time, at least over the follow-up period of 72 mo in this study.

Multivariate analysis to identify the risk factors of LDA-associated peptic ulcer in both sexes

Table 5 shows the results of multivariate analyses to identify the risk factors of LDA-associated peptic ulcer

Table 5 Multivariate analysis to identify risk factors of LDA-associated gastroduodenal ulcer in male and female patients

Factor	Odds ratio	95% CI	*P*-value
Male patients (n = 211)			
PPIs	0.069	0.009-0.555	0.0120
H2RAs	0.498	0.256-0.967	0.0396
History of peptic ulcer	3.745	1.734-8.088	0.0008
Female patients (n = 123)			
H2RAs	0.255	0.077-0.839	0.0245
History of peptic ulcer	6.439	1.874-22.131	0.0031
Age ≥ 70 yr	8.441	1.797-33.649	0.0069

Odds ratio: Prevalence odds ratio.

in both sexes. In male patients, a history of peptic ulcer (prevalence ORs 3.745, 95% CI: 1.734-8.088, $P = 0.0008$) was found to be associated with an increase in the risk, and a history of PPIs (prevalence ORs 0.069, 95% CI: 0.009-0.555, $P = 0.0120$) and/or H2RAs (prevalence ORs 0.498, 95% CI: 0.256-0.967, $P = 0.0396$) use was found to be associated with a decrease in the risk. In female patients, a history of peptic ulcer (prevalence ORs 6.439, 95% CI: 1.874-22.131, $P = 0.0031$) and age greater than 70 years (prevalence ORs 8.441, 95% CI: 1.797-33.649, $P = 0.0069$) were associated with an increase in the risk. Statistical analysis with respect to the use of PPIs could not be performed in female patients, because there was no female patient taking PPIs who was diagnosed as having LDA-associated peptic ulcer.

DISCUSSION

The present study demonstrated gender differences in the clinical features of LDA-associated gastroduodenal ulcer in Japanese patients. Previous reports have indicated age greater than 65 years, previous history of peptic ulcer[4,5], use of other NSAIDs[6] and *H. pylori* infection[7] as some of the risk factors of LDA-associated peptic ulcer, and the concomitant use of antisecretory drugs as a factor reducing the risk of LDA-associated peptic ulcer[5,8,9]. In this study, a history of peptic ulcer was found to be the risk factor of LDA-associated peptic ulcer common to both sexes. In female patients, advanced age or aging was found to be another significant factor. In elderly patients, gastric mucosal defenses are impaired because of the reduced mucus and bicarbonate secretion, and also the significant decrease in gastric mucosal perfusion. The reduced gastric mucosal defenses coupled with a reduced gastric prostaglandin biosynthesis may account for the higher susceptibility of the mucosa to damage-inducing agents[10]. In general, female subjects are at a relatively reduced risk of developing gastric ulcers[11]. In animal experimental models, female sex hormones have been demonstrated to show significant antiulcer activity and to promote healing of drug-associated ulcers (aspirin, indomethacin)[12,13]. Estrogen has also been reported to reduce the incidence of *H. pylori*-associated gastric mucosal injuries, despite having no effect on the *H. pylori* infection status. Female sex hormones may exert a protective effect against LDA-associated mucosal injury. In female patients of advanced age, the gradual decrease in the serum levels of female sex hormones after menopause and with advancing age, coupled with the reduced gastric mucosal defenses may be responsible for the increase in the risk of LDA-associated peptic ulcer.

In addition, time from the start of LDA until the diagnosis of LDA-associated peptic ulcer by endoscopy was shorter in the female patients. This gender difference, akin to the significantly higher relative risk and short time-to-onset of alcohol-related liver disease in women as compared to men for any given level of alcohol intake[14], is yet to be well elucidated. The incidence of peptic ulcer seemed almost constant and does not decrease with time, at least over the follow-up period of 72 mo in this study (Table 3). It has been suggested that NSAID-associated gastrointestinal bleeding occurs mainly within the first few weeks of treatment[15], which is a shorter period than that reported in LDA users. We should recognize that LDA-associated peptic ulcer may not occur for several years; therefore, it is important to continue antisecretory therapy, especially in high-risk patients. Future prospective cohort studies are needed to confirm this assumption.

COMMENTS

Background

The gender differences in the clinical manifestations of low-dose aspirin (LDA)-associated gastroduodenal mucosal injury have not been well-studied.

Research frontiers

The authors hypothesized that there were gender differences in clinical features of LDA-associated peptic ulcer, and it might be useful to identify the risk factors of LDA associated ulcer in both sexes.

Innovations and breakthroughs

In female patients, age greater than 70 years was found to be a significant risk factor of LDA associated peptic ulcer in addition to a history of peptic ulcer, and the time to diagnosis as having LDA-associated peptic ulcer by endoscopy was significantly shorter than that in the male patients.

Applications

By understanding the gender differences in clinical features of LDA-associated ulcer, this study may represent a future strategy for the prevention of LDA-associated peptic ulcer.

Terminology

Special attention should be paid to aged female patients taking LDA. People should also recognize that LDA-associated peptic ulcer may not occur for several years; therefore, it is important to continue antisecretory therapy, especially in high-risk patients.

Peer review

This study is adequately designed and performed. It means a contribution in a topic of high relevance.

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