Original Article

Current states of prevention of drug-induced gastroduodenal ulcer in real clinical practice: a cross-sectional study

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Non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin (LDA) are the most common causes of drug-induced gastroduodenal ulcer and We investigated preventive treatment with use of concomitant anti-ulcer drugs and the clinical features of gastroduodenal ulcer in cases treated with these drugs. Patients with gastroduodenal ulcer and patients with bleeding were classified into 3 groups: LDA, non-aspirin NSAIDs, and those taking neither aspirin nor NSAIDs. Chronological changes over the past 16 years (1st–5th period) were investigated. The status of prevention of ulcer and clinical features were examined. From January 2002 to December 2018, the ratio of all patients taking NSAIDs and LDA increased significantly until 3rd period ($p<0.05$), but then started to decrease in 4th period; and the percentage of all patients taking NSAIDs and LDA decreased significantly ($p<0.05$) until 5th period. Among the 292 patients with gastroduodenal ulcer and the 121 patients with a bleeding ulcer taking NSAIDs and LDA, 16 (5.5%) and 9 (7.4%), respectively, were receiving preventive treatment with concomitant anti-ulcer drugs. The percentages of patients taking LDA and other antiplatelet drugs in patients with bleeding gastroduodenal ulcer were significantly higher than those in patients with non-bleeding. In conclusion, although the percentages of patients with gastroduodenal ulcer taking NSAIDs or LDA have not recently increased in real-world practice, preventive treatment in these patients is still low. This low rate of prevention suggests the need to enlighten physicians about preventive treatment because drug withdrawal of LDA has a high risk of cardiovasculr and cerebrovascular events.

***Key Words*:** **gastroduodenal ulcer, low-dose aspirin, non-steroidal anti-inflammatory drugs, prevention**

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain in rheumatoid arthritis or orthopedic disease and are the most common cause of drug-induced gastroduodenal ulcer.[1,2] Low-dose aspirin (LDA) is now commonly used for prevention of cardiovascular and cerebrovascular events with the advent of aging of society.[3–5] Worldwide trials have shown that LDA at 75–325 mg/day or other antiplatelet regimens offers beneficial protection against myocardial infarction, stroke, and death.[4] In contrast, a very low dose of aspirin (10 mg daily) decreases gastric mucosal prostaglandin levels and causes significant gastric mucosal damage,[6] and this may have increased the incidence of LDA-induced gastrointestinal mucosal injury.[7–10]

In cases of drug-induced gastroduodenal ulcer bleeding, drug withdrawal including LDA involves a high risk of cardiovascular and cerebrovascular events. Therefore, prevention of gastroduodenal ulcer bleeding in patients taking drugs including NSAIDs and LDA is clinically important,[11,12] but it is unclear to what extent preventive treatment is being used in such cases in real world practice. Therefore, in the present study, we investigated chronological changes in use of NSAIDs and LDA in patients with gastroduodenal ulcer taking NSAIDs and LDA and examined the current status of prevention for these cases in clinical practice.

Methods

Patients. Among 44,620 patients who underwent gastrointestinal endoscopy between January 2002 and December 2018 (excluding cases with ulcer scar, stomal ulcer and severe complications), 2,437 patients with gastroduodenal ulcer (1,702 with gastric ulcer and 735 with duodenal ulcer; ratio 2.37:1), including 622 (479 with gastric ulcer and 143 with duodenal ulcer; ratio 3.32:1) with bleeding ulcer, were diagnosed at Tokyo Medical University Ibaraki Medical Center and included in the study. Informed consent was obtained from all subjects, and the experimental protocol was approved by the Ethics Committee of Tokyo Medical University Ibaraki Medical Center.

The 2,437 patients were classified into three groups: those taking LDA, those taking non-aspirin NSAIDs (hereinafter referred to as NSAIDs), and those taking neither LDA nor NSAIDs. Patients receiving a combination of LDA and NSAIDs were placed in the NSAIDs group. Chronological changes in the percentage of each group and the change in percentages over 16 years (1st–5th period) were investigated.

In a sub-analysis, among 873 patients with gastroduodenal ulcer (606 with gastric ulcer and 267 with duodenal ulcer; ratio 2.34:1) of 21,025 patients who underwent gastrointestinal endoscopy in the 8 years from January 2011 to December 2018, we evaluated 292 patients with gastroduodenal ulcer (214 with gastric ulcer and 68 with duodenal ulcer) taking NSAIDs or LDA, including 121 with a bleeding ulcer. Use of preventive treatment with concomitant anti-ulcer drugs and clinical features of cases under preventive treatment were examined.

Statistical analysis. Data are expressed as mean ± SD. Categorical variables were compared by chi-square test, and continuous variables by Mann-Whitney test, with $p<0.05$ considered to be significant.

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Results

Chronological changes in patients with gastroduodenal ulcer taking NSAIDs and LDA. For the patients with all or bleeding gastroduodenal ulcer, the mean ages of those taking LDA and NSAIDs were higher than those taking neither LDA nor NSAIDs ($p<0.05$). In these patients, the male/female ratio in those taking NSAIDs was lower than those in the other groups ($p<0.05$) (Table 1).

From January 2002 to December 2018, the percentage of all patients taking NSAIDs and LDA increased significantly until 3rd period ($p<0.05$), but then started to decrease in 4th period; and the percentage of all patients taking NSAIDs and LDA decreased significantly ($p<0.05$) until 5th period. In patients with a bleeding ulcer, use of LDA increased until 4th period and then started to decrease in 5th period, but without significance; and the percentage of all patients taking NSAIDs and LDA decreased until 5th period, again with no significance (Table 2A and B, Fig. 1 and 2).

Preventive treatment in patients with gastroduodenal ulcer taking NSAIDs and LDA. Among the 292 patients with gastroduodenal ulcer taking NSAIDs and LDA, 16 (5.5%) were receiving preventive treatment with concomitant anti-ulcer drugs, and 276 (94.5%) were not receiving this treatment. In the 107 patients with a bleeding ulcer taking NSAIDs and LDA, 9 (7.4%) were receiving preventive treatment, and 112 (92.6%) were not (Table 3). In the 16 cases receiving preventive treatment, 11 (69%) and 5 (31%) were taking a half dose and a full dose of a proton pump inhibitors (PPIs) (Table 4). In patients with non-bleeding and bleeding gastroduodenal ulcer, 85.7% and 22.2% were taking a single NSAID, and 14.3% and 77.8% were taking LDA or another antiplatelet drug, respectively. The ratio of bleeding gastroduodenal ulcer taking LDA or another antiplatelet drug were higher than that of non-bleeding cases, significantly (Table 5).

Discussion

The efficacy of LDA for prevention of cardiovascular and cerebrovascular diseases has been established,[3–5] but the risks of peptic ulcer complications increase in association with LDA use.[6–10] A meta-analysis of 24 randomized controlled trials revealed that gastrointestinal hemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo.[7] Recent reports also have indicated that low-dose aspirin cause not only gastroduodenal mucosal injury but also small bowel injury with high frequency.[13,14]

We investigated the chronological changes in use of NSAIDs and LDA in patients with gastroduodenal ulcer since 2002. The percentage of these patients taking NSAIDs or LDA initially increased, but has decreased in recent years. High doses of histamine H2 receptor antagonist (H2RAs), PPIs or prostaglandin analogs are recommended for prevention of NSAID or LDA-induced gastroduodenal ulcer, and PPIs are especially used widely as first-line drugs.[11,12] The spread of preventive use of PPIs may have caused the chronological changes in use of LDA and NSAIDs found in the current study. However, in real world practice in our hospital, only 6% of patients with gastroduodenal ulcer taking NSAIDs and LDA were receiving preventive treatment with concomitant anti-ulcer drugs over the last 8 years, which indicates that use of this treatment is still insufficient.

Prevention of ulcer using PPIs is recommended, but some previous reports have suggested that this treatment is insufficient.[15,16] For example, it has been reported that 13% of cases had recurrence of gastroduodenal ulcer after treatment with 15 mg lansoprazole.[17] In cases of LDA-induced gastroduodenal ulcer and bleeding, discontinuation of LDA can increase the risk of cardiovascular and cerebrovascular diseases,[18–20] and continuation of LDA is recommended.[12] Sung, *et al.*[20] investigated continuation of aspirin therapy with PPIs after endoscopic control of ulcer bleeding, and found that this was not inferior to stopping aspirin. The results showed that patients who continued aspirin had lower

Table 1. Age and male/female ratios in each group of patients

Group	Item	LDA	NSAIDs	LDA (–) NSAIDs (–)
All patients	Age (years)	69.2 ± 15.4*	66.4 ± 14.2*	54.3 ± 15.5
	Gender (M/F)	1.84	1.17*	2.45
Patients with bleeding	Age (years)	71.1 ± 13.5*	67.4 ± 16.3*	60.8 ± 14.4
	Gender (M/F)	1.82	1.05	2.13

*$p<0.05$ for comparison between each patient group.

Table 2A. The number of cases and ratio (%) of non-NSAIDs non LDA users, NSAIDs users, and LDA users with gastroduodenal ulcer

Period		NSAIDs (–) LDA (–)	NSAIDs	LDA	NSAIDs + LDA
1st period	2002.Jan.–2005.Dec.	397 (72.9)	105 (19.3)	42 (7.8)	147 (27.1)
2nd period	2006.Jan.–2008.Dec.	336 (67.7)	118 (23.7)	43 (8.6)	161 (32.3)
3rd period	2009.Jan.–2011.Dec.	300 (65.3)	94 (20.5)	65 (14.2)	159 (34.7)
4th period	2012.Jan.–2014.Dec.	271 (71.7)	59 (15.6)	48 (12.7)	107 (28.7)
5th period	2015.Jan.–2018.Dec.	408 (72.9)	97 (17.3)	54 (9.8)	151 (27.1)

Table 2B. The number of cases and ratio (%) of non-NSAIDs non LDA users, NSAIDs users, and LDA users with bleeding gastroduodenal ulcer

Period		NSAIDs (–) LDA (–)	NSAIDs	LDA	NSAIDs + LDA
1st period	2002.Jan.–2005.Dec.	78 (62.9)	34 (27.4)	12 (9.6)	46 (37.1)
2nd period	2006.Jan.–2008.Dec.	67 (57.3)	31 (26.5)	19 (16.2)	50 (42.7)
3rd period	2009.Jan.–2011.Dec.	56 (60.2)	22 (23.7)	15 (16.1)	37 (39.8)
4th period	2012.Jan.–2014.Dec.	66 (60.6)	21 (19.3)	22 (20.2)	43 (39.4)
5th period	2015.Jan.–2018.Dec.	109 (62.6)	37 (21.3)	28 (16.1)	65 (37.4)

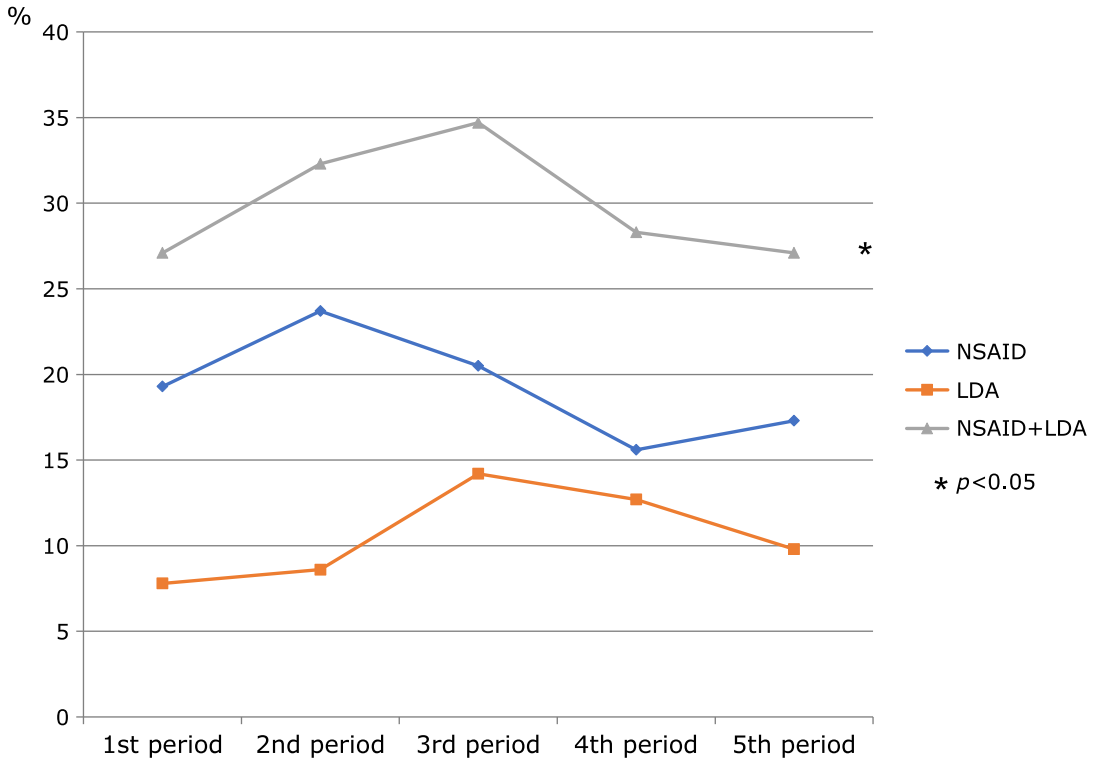

Fig. 1. Chronological changes in use of NSAIDs and LDA in all patients with gastroduodenal ulcer. *$p<0.05$ for comparison between each patient group.

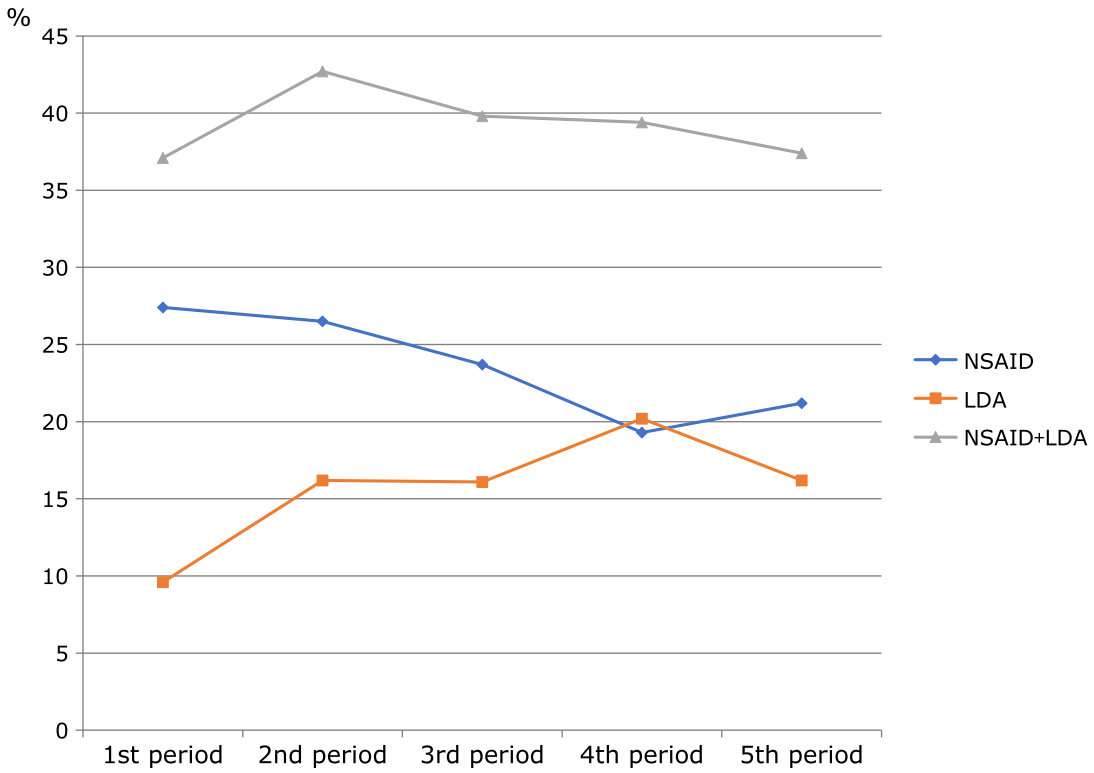

Fig. 2. Chronological changes in use of NSAIDs and LDA in patients with bleeding due to gastroduodenal ulcer.

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Table 3. Rate of use of preventive treatment in patients with gastroduodenal ulcer taking NSAIDs and LDA

Patients	Prevention (+)	Prevention (–)
Gastroduodenal ulcer (n = 292)	16 (5.5%)	276 (94.5%)
Gastroduodenal ulcer bleeding (n = 121)	9 (7.4%)	112 (92.6%)

Table 4. Details of treatment with anti-ulcer drugs in 16 cases receiving preventive treatment

Dose	Total Cases	Drug	Number of Cases (%)
Low dose	11 cases (69%)	Lansoprazole (15 mg)	10 (62.5%)
		Omeprazole (10 mg)	1 (6.3%)
High dose	5 cases (31%)	Omeprazole (20 mg)	2 (12.5%)
		Rabeprazole (20 mg)	2 (12.5%)
		Esomeprazole (20 mg)	1 (6.3%)

Table 5. Causative drugs in patients with non-bleeding and bleeding gastroduodenal ulcer

Patients	Causative drugs	Cases (%)	
Gastroduodenal ulcer (non-bleeding) (n = 7)	NSAIDs	6 (85.7%)*	
	NSAIDs + LDA	1 (14.3%)	
Gastroduodenal ulcer (bleeding) (n = 9)	NSAIDs	2 (22.2%)	
	LDA + Thienopyridine	2 (22.2%)	77.80%
	LDA	2 (22.2%)	
	NSAID + LDA + Thienopyridine	1 (11.1%)	
	LDA + Thienopyridine + Warfarin	1 (11.1%)	
	Thienopyridine	1 (11.1%)	

*p<0.05 for the comparison between non-bleeding and bleeding cases.

all-cause mortality and lower mortality attributable to cardiovascular, cerebrovascular, or gastrointestinal complications, compared to patients who stopped aspirin.[20] Since stopping LDA after gastroduodenal bleeding increases the risk of cardiovascular and cerebrovascular diseases, more thorough preventive treatment is needed. Recently, the efficacy of vonoprazan for prevention of NSAID and LDA-induced gastroduodenal ulcer has been reported in Japan.[21,22]

In cases under treatment with concomitant anti-ulcer drugs, we found that a significant higher rate of use of single NSAIDs in non-bleeding cases than in bleeding cases, and we also found a significant higher rate of use of LDA or other antiplatelet drugs in bleeding cases. These results may indicate that, in contrast to patients taking LDA or other antiplatelet drugs, those taking a single NSAID have a lower risk of gastroduodenal bleeding while under preventive treatment. These results also suggest that greater attention to gastroduodenal bleeding is needed in patients taking LDA or other antiplatelet drugs with concomitant preventive therapy.

This study has several limitations. First, it was retrospective observational study in single center. Second, the sample size was small. In the next study, if possible, the incidence rate of drug-induced peptic ulcer with and without the prevention with PPI should be examined in the multicenter cohort study. Furthermore, we could not demonstrate the data analysis as to the relationship between preventive treatment and the decrease of ulcer or bleeding. In the next study, we would like to demonstrate the relationship between preventive treatment and the decrease of ulcer or bleeding.

In conclusion, although preventive treatment with PPIs is recommended, we found that this treatment is insufficiently applied in real world practice, and that few patients with gastroduodenal ulcer are receiving concomitant anti-ulcer drugs. However, stopping LDA after gastroduodenal bleeding increases the risk of cardiovascular and cerebrovascular diseases, and therefore, more thorough preventive treatment is needed in these cases.

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Abbreviations

H2RA	histamine H2 receptor antagonist
LDA	low-dose aspirin
NSAIDs	non-steroidal anti-inflammatory drugs
PPI	proton pump inhibitor

Data Availability

All data generated or analyzed during this study are included in this article.

Conflicts of Interest

No potential conflicts of interest were disclosed.

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