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Usefulness of anti-ulcer drugs for the prevention and treatment of peptic ulcers induced by low doses of aspirin

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Abstract

AIM: To investigate the usefulness of anti-ulcer drugs for the prevention and treatment of low-dose aspirin-induced peptic ulcer.

METHODS: Upper gastrointestinal endoscopy was performed in 68 patients receiving daily low-dose aspirin (81 or 100 mg/day). The endoscopic findings were classified according to the Lanza score, and the scores were compared between groups categorized according to the concomitant use of anti-ulcer drugs and the types of drugs used. In another study, 31 hemorrhagic peptic ulcer patients who had been receiving low-dose aspirin were enrolled. The patients were randomly classified into the proton pump inhibitor (PPI)-treated group and the H2 receptor antagonist (H2RA)-treated group. The administration of low-dose aspirin was continued concomitantly, and endoscopic examinations were performed 8 wk later.

RESULTS: The Lanza scores (mean ± SD) of the gastro-mucosal lesions were 1.0 ± 1.9 and 1.9 ± 2.3 in 8 and 16 patients receiving prevention therapy with a PPI and an H2RA, respectively. Both scores were significantly smaller than the scores in 34 patients who were not receiving prevention therapy (4.7 ± 1.0) and in 10 patients receiving cytoprotective anti-ulcer drugs (4.3 ± 1.6). In the prospective study, 18 and 13 patients received a PPI and an H2RA, respectively. Endoscopic examinations revealed that the tissue in the region of the gastro-mucosal lesions had reverted to normal in all patients in the PPI-treated group and in 12 patients (92%) in the H2RA-treated group; no significant differences were observed between the groups.

CONCLUSION: H2RA therapy was effective for both the prevention and treatment of low-dose aspirin-induced peptic ulcer, similar to the effects of PPIs, while cytoprotective anti-ulcer drugs were ineffective in preventing ulceration.

Key words: Hemorrhagic ulcer; H2 receptor Antagonist; Low-dose aspirin; Peptic ulcer; Proton pump inhibitor

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INTRODUCTION

Two major causes of peptic ulcers are infection with *Helicobacter pylori* (*H pylori*) and the administration of non-steroidal anti-inflammatory drugs (NSAIDs). Recently, much attention has been paid to NSAID-induced peptic ulcers, since the trend toward *H pylori* eradication using proton pump inhibitors (PPIs) and antibiotics is likely to reduce the incidence of *H pylori*-induced peptic ulcers in the future. Moreover, the increasing proportion of elderly individuals among the Japanese population is likely to produce a simultaneous increase in the prescription

of NSAIDs for the treatment of pain arising from osteoporosis and/or osteoarthritis. This trend may highlight the significance of NSAID-induced peptic ulcers. Low-dose aspirin has also been shown to induce peptic ulcers, similar to the effects of regular-dose aspirin and other NSAIDs[1]; this finding suggests that NSAID-induced peptic ulcers may become more common among the elderly population, since many patients receive antithrombotic therapy using low-dose aspirin for the treatment of cardiovascular diseases. Previously, we reported that NSAIDs were associated with hemorrhagic peptic ulcers in 28% of the patients seen between 2001 and 2004; the rate of patients receiving low-dose aspirin in this population was 27%, while the rates of patients receiving regular-dose aspirin, loxoprofen, diclofenac and other NSAIDs were 6%, 16%, 10% and 21%, respectively[1]. These data suggest that among the various NSAIDs in use, low-dose aspirin is the most important drug provoking peptic ulcers in Japan.

Infection with *H pylori* is frequently found in patients with NSAID-induced peptic ulcers, including those with low-dose aspirin-induced ulcers. According to our previous survey[1], a total of 82% of patients with hemorrhagic peptic ulcers tested positive for *H pylori* infection; the positivity rate was higher among those not treated with NSAIDs (88.6%) than among those receiving NSAIDs (67.2%). Of note, 62.5% of the patients with hemorrhagic peptic ulcers induced by low-dose aspirin tested positive for *H pylori*[1]. However, whether *H pylori* eradication prevents the development of peptic ulcers induced by low-dose aspirin remains controversial[2]. Chan *et al*[3] reported that both *H pylori* eradication and PPI administration were effective in preventing peptic ulcers induced by low-dose aspirin. On the other hand, Lai *et al*[4] revealed that hemorrhage recurred in more than 10% of the patients with low-dose aspirin-induced peptic ulcers, even after *H pylori* eradication, whereas PPI administration was effective in reducing the risk of recurrence. A therapeutic strategy to prevent peptic ulcers induced by NSAIDs, especially low-dose aspirin, is needed.

In the present study, we evaluated the efficacies of various anti-ulcer drugs (PPIs, H2RA and cytoprotective drugs) for the prevention and treatment of peptic ulcers induced by low-dose aspirin, by comparing the endoscopic findings of the patients to establish a therapeutic strategy for low-dose aspirin-induced peptic ulcers in Japanese patients.

MATERIALS AND METHODS

Study-1

Patients receiving daily low-dose aspirin (81 or 100 mg/day) and undergoing an upper gastrointestinal endoscopy at Saitama Medical University Hospital between February 2001 and September 2006 were enrolled in the study. Patients receiving NSAIDs other than aspirin and/or receiving regular-dose aspirin (from 1.0 to 4.5 g/day) were excluded from the analysis. Patients with malignancies or those who had undergone a gastrectomy were also excluded. The endoscopic findings were classified according to the Lanza score, as show in Table 1[5]. The scores were compared between groups categorized according to the concomitant use of anti-ulcer drugs and the types of drugs used.

Table 1 Classification of endoscopic findings according to the Lanza score[5]

Score	Endoscopic findings
0	No lesion
1	Hemorrhagic erosion
2	One or two erosions
3	3-10 erosions
4	More than 10 erosions
5	Ulcer

Study-2

The subjects comprised hemorrhagic peptic ulcer patients who had been receiving low-dose aspirin daily and who had been admitted to Saitama Medical University Hospital between February 2001 and March 2008. The exclusion criteria were similar to those used in Study-1: patients receiving NSAIDs other than aspirin and/or regular-dose aspirin and those with malignancies or who had undergone a gastrectomy at enrolment. Informed consent was obtained from all patients, and the subjects were randomly classified into two groups. The patients classified as the PPI-treated group were given either lansoprazole (15 or 30 mg, daily), rabeprazole sodium (10, 20 or 40 mg, daily) or omeprazole (20 mg, daily). In contrast, the patients in the H2RA-treated group were given famotidine (40 mg, daily). In all patients, the administration of low-dose aspirin was continued concomitantly with the PPI or famotidine therapy. Infection with *H pylori* was determined using a serum antibody test (AP-960; Scimed Life Systems/Boston Scientific Corp, Natick, MA, USA) or a culture of gastric mucosal specimens obtained during an endoscopic examination. *H pylori* eradication with the administration of lansoprazole (60 mg, daily), amoxicillin hydrate (1500 mg, daily) and clarithromycin (800 mg, daily) was performed for 7 d in patients with a positive infection status within 2 wk of the occurrence of peptic ulcer hemorrhage. The therapeutic efficacy of *H pylori* eradication was assessed by the urea breath test 8 wk later. An upper gastrointestinal endoscopy was performed 8 wk after the initiation of PPI or famotidine therapy. The ulcer was diagnosed as healed once scar formation at the site of the lesion was complete.

Statistical Analysis

The Mann-Whitney *U* test and the Fisher's exact test were used to analyze the data. Statistical significance was defined as $P < 0.05$.

RESULTS

Study-1

Sixty-eight patients (45 men and 23 women) between

Table 2 Anti-ulcer drugs used in patients enrolled in study-1

Type of drug	Drug name	Doses (/day)	Number of patients
None			34
PPIs			8
	Rabeprazole sodium	10 mg	3
	Lansoprazole	30 mg	2
	Lansoprazole	15 mg	1
	Omeprazole	20 mg	2
H2RAs			16
	Famotidine	40 mg	1
	Famotidine	20 mg	8
	Famotidine	10 mg	1
	Lafutidine	20 mg	2
	Nizatidine	300 mg	2
	Ranitidine hydrochloride	75 mg	1
	Cimetidine	100 mg	1
Cytoprotective anti-ulcer drugs			10
	Rebamipide	300 mg	2
	Rebamipide	200 mg	1
	Rebamipide	100 mg	1
	Azulensulfonate sidium + L-Glutamine	2 g	2
	Teprenone	1.5 g	1
	Polaprezinc	150 mg	1
	Sofalcone	300 mg	1
	Alginate sodium	180 mL	1

the ages of 25 and 88 years were enrolled in the study. Thirty-four patients received no anti-ulcer drugs, while 8, 16 and 10 patients were given PPIs, H2RAs and cytoprotective anti-ulcer drugs, respectively. The types and doses of the anti-ulcer drugs are shown in Table 2. Duration of daily low-dose aspirin therapy ranged from 1 to 3650 d, however, therapy duration (days; mean ± SD) did not differ in patients receiving and not receiving anti-ulcer drugs (898 ± 1384 and 1165 ± 1389, respectively). In the case of patients receiving anti-ulcer drugs, the prevention therapies were initiated simultaneously with low-dose aspirin administration. Anti-platelet and anticoagulant drugs were used in 5 and 1 patients receiving and not receiving anti-ulcer drugs, respectively. No differences in age or sex were observed among the patients not treated with anti-ulcer drugs and those receiving PPI, H2RA or cytoprotective anti-ulcer drugs (Table 3). However, the endoscopic scores were significantly smaller in patients receiving PPIs and H2RAs, compared with those receiving cytoprotective anti-ulcer drugs and those not receiving anti-ulcer drugs. A grade 5 endoscopic score was observed in 31 of 34 patients (91%) not receiving anti-ulcer drugs and in 8 of 10 patients (80%) receiving cytoprotective anti-ulcer drugs, while the grades ranged between 0 and 3 in 11 of 16 patients (69%) receiving H2RAs and in 7 of 8 patients (88%) receiving PPIs. The scores in patients receiving PPIs and in those receiving H2RAs were statistically similar. In addition, no differences were observed between the scores in 5 patients receiving regular-dose H2RAs and in 11 patients receiving low-dose H2RAs. Moreover, the scores in patients receiving cytoprotective anti-ulcer drugs and in those not receiving anti-ulcer drugs were similar. One 72-year-old male patient had an endoscopic score of grade 5 despite the use of a PPI. *H pylori* infection was not detected in this patient, but a coronary artery bypass grafting procedure had been performed 39 d prior to the endoscopic examination, and the patient had been receiving daily doses of warfarin in addition to low-dose aspirin since that time.

Study-2

Forty patients were enrolled in the study: 20 patients in the PPI-treatment group and 20 patients in the H2RA-treatment group. An endoscopic examination was performed at 8 wk in 18 patients (13 men and 5 women) aged 69.2 ± 13.4 years (mean ± SD) in the PPI-treatment group and in 13 patients (10 men and 3 women) aged 69.7 ± 9.5 years in the H2RA-treatment group; the 9 remaining patients were transferred to other hospitals prior to endoscopic examination. A positive *H pylori* infection status was seen in 12 and 10 patients (67% and 77%) in the PPI-treatment and H2RA-treatment groups, respectively; *H pylori* infection rate was similar in both groups. *H pylori* eradication was achieved in all patients who had a positive *H pylori* infection status. Endoscopic examinations performed at 8 wk revealed that the peptic ulcers had completely healed in 18 patients (100%) in the PPI-treatment group and in 12 patients (92%) in the H2RA-treatment group; no difference in therapeutic efficacy was seen between the two groups. The peptic ulcer in one patient with a positive *H pylori* infection status in the H2RA-treatment group had not completely healed at 8 wk. This patient had repeatedly received loxoprofen for the treatment of a headache 1 wk prior to the endoscopic examination, suggesting that peptic ulcers might recur in the presence of loxoprofen administration, even if the low-dose aspirin-induced ulcer had healed during famotidine therapy. There were 3 and 6 patients with a negative *H pylori* infection status in the H2RA-treatment and PPI-treatment groups, respectively. Peptic ulcers were completely healed in all these patients.

DISCUSSION

In the US and Europe, drugs such as PPIs[6], prostaglandins[7] and regular-dose H2RAs[8] have been reported to be effective in the prevention of NSAID-induced peptic ulcers, and PPIs and prostaglandins have been reported to effectively attenuate such ulcers[6]. In addition, studies conducted in Hong Kong and the US have revealed that both *H pylori* eradication[3] and PPI treatment[4] are useful in preventing the recurrence of hemorrhagic peptic ulcers induced by low-dose aspirin. In Japan, however, the administration of PPIs, H2RAs and prostaglandins for the prevention of peptic ulcers induced by NSAIDs and low-dose aspirin is not covered by medical insurance, although the use of these drugs for the treatment of peptic ulcers is covered. Among these drugs, PPIs and prostaglandins are widely accepted as the most effective therapeutic agents for NSAID-induced peptic ulcers, however, prostaglandins are seldom used due to their adverse effects such as abdominal pain and diarrhea. Thus, in Japan, many

Table 3 Endoscopic findings classified according to the Lanza score in patients receiving low-dose aspirin with or without anti-ulcer drugs

Number of patients	Sex M:F	Age (yr) (mean ± SD)	Lanza scores (Number of patients)						Mean scores
			0	1	2	3	4	5	
No anti-ulcer drugs									
34	24:10	69.4 ± 11.2	1	0	1	0	1	31	4.74[1]
Cytoprotective drugs									
10	8:2	67.9 ± 8.6	1	0	0	1	0	8	4.30[1]
H2RAs									
16	7:9	67.8 ± 14.0	7	3	1	0	0	5	1.88[1]
At regular doses									
5	2:3	69.6 ± 10.8	2	1	1	0	0	1	1.60[1]
Less than regular doses									
11	5:6	66.9 ± 15.6	5	2	0	0	0	4	2.00[1]
PPIs									
8	6:2	62.0 ± 17.0	6	0	0	1	0	1	1.00[1]

[1]$P < 0.05$ *vs* both no anti-ulcer drugs and cytoprotective drugs, according to the Mann-Whitney *U* test.

physicians usually use PPIs for the treatment of peptic ulcers induced by NSAIDs and low-dose aspirin. For the prevention of peptic ulcers, cytoprotective anti-ulcer drugs other than prostaglandins are commonly used, although no evidence supporting this use has been reported in the medical literature. Therefore, a therapeutic strategy for the treatment and prevention of peptic ulcers induced by NSAIDs, especially low-dose aspirin, should be established for Japanese patients.

Thus, we performed a retrospective study (Study-1) to clarify the efficacy of various anti-ulcer drugs to prevent peptic ulcers induced by low-dose aspirin and a prospective study (Study-2) to compare the therapeutic efficacies of PPIs and H2RAs for treating such ulcers. The retrospective study revealed that H2RAs effectively prevented peptic ulcers induced by low-dose aspirin to a degree similar to that of PPIs, however, cytoprotective drugs were not effective in preventing peptic ulcers. To our surprise, H2RA administration at doses less than the regular dose was also effective in preventing low-dose aspirin-induced peptic ulcers. Furthermore, the prospective study demonstrated that the therapeutic efficacies of PPIs and H2RAs at regular doses were almost equivalent. The secretion of gastric acids from the gastric mucosa has been shown to be lower in Japanese patients than in European and American patients[9,10], since marked atrophy of the gastric mucosa is often found in many Japanese patients due to the prevalence of *H pylori* infection. Thus, low-dose H2RAs, such as famotidine 20 mg daily, seem to be effective in the prevention of peptic ulcers induced by low-dose aspirin, and regular-dose H2RAs, such as famotidine 40 mg, may be sufficient to treat such peptic ulcers in Japanese patients. However, it should be noted that grade-5 endoscopic findings were observed in a 72-year-old patient in Study-1 receiving both warfarin and low-dose aspirin despite concomitant prevention therapy with a PPI. In addition, peptic ulcer healing did not occur in one patient receiving loxoprofen as well as low-dose aspirin in the H2RA-treated group in Study-2. The usefulness of H2RAs for the treatment and prevention of low-dose aspirin-induced peptic ulcers should be further investigated, focusing on elderly patients and those receiving warfarin as well as NSAIDs[11]. Moreover, the therapeutic and prevention efficacy of H2RA should be studied in relation to *H pylori* infection status, therapeutic effect of *H pylori* infection, history of upper gastrointestinal diseases and the types of peptic ulcer such as acute and chronic disorders in future research.

In conclusion, H2RA therapy was effective for both the prevention and treatment of low-dose aspirin-induced peptic ulcers, similar to the effects of PPIs, while cytoprotective anti-ulcer drugs were ineffective in preventing peptic ulcers. Considering the cost and adverse effects of PPIs and prostaglandins, H2RA may be the most beneficial anti-ulcer drug for the prevention and treatment of peptic ulcers induced by low-dose aspirin in Japan.

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COMMENTS

Background

The incidence of low-dose aspirin-induced peptic ulcer seems to be increasing in Japan in conjunction with the increasing proportion of elderly individuals, in whom metabolic syndrome frequently develops. However, a therapeutic and prevention strategy for such peptic ulcers has not yet been established.

Research frontiers

The effect of *Helicobacter pylori* (*H pylori*) eradication in the prevention of peptic ulcers induced by low-dose aspirin remains controversial. Chan *et al*[3] reported that both *H pylori* eradication and proton pump inhibitor (PPI) administration were effective in preventing peptic ulcers induced by low-dose aspirin. On the other hand, Lai *et al*[4] revealed that hemorrhage recurred in more than 10% of patients with low-dose aspirin-induced peptic ulcers, even after *H pylori* eradication, whereas PPI administration was effective in reducing the risk of recurrence.

Innovations and breakthroughs

H2 receptor antagonist (H2RA) was effective in both the prevention and treatment of low-dose aspirin-induced peptic ulcers, similar to the effects of

PPIs, while cytoprotective anti-ulcer drugs were ineffective in preventing ulcers.

Applications

Considering the cost and adverse effects of PPIs and prostaglandins, H2RAs may be the most beneficial anti-ulcer drugs for the prevention and treatment of peptic ulcers induced by low-dose aspirin in Japan.

Terminology

Low-dose aspirin: aspirin at regular doses (from 1.0 to 4.5 g/day) is administered to patients with fever, headache and arthralgia. In contrast, daily low-dose aspirin (81 or 100 mg/day) is used as antithrombotic therapy for patients with cardiovascular diseases.

Peer review

The incidence of low-dose aspirin-induced peptic ulcers is increasing in Japan, but the evidence is still lacking. In this paper, the authors evaluated the efficacies of various anti-ulcer drugs for the prevention and treatment of low-dose aspirin-induced peptic ulcers. The author concluded that the efficacies of H2RAs and PPIs for the prevention and treatment of L-Asp-induced peptic ulcers.

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