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Assessing the efficacy of famotidine and rebamipide in the treatment of gastric mucosal lesions in patients receiving long-term NSAID therapy (FORCE—famotidine or rebamipide in comparison by endoscopy)

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Background. Nonsteroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori infection are major causes of gastric mucosal lesions. In Japan, histamine-2 receptor antagonists are frequently prescribed, but the literature regarding their efficacy is limited. In this study, we compare the effects of famotidine and rebamipide on NSAID-associated gastric mucosal lesions using upper gastrointestinal endoscopy. ***Methods.*** This study examined 112 patients taking NSAIDs for either gastric hemorrhage or erosion. Before treatment, the patients were assessed by endoscopy. Using blind randomization, patients were divided into two groups: group F (famotidine, 20 mg/day) and group R (rebamipide, 300 mg/day). Efficacy was examined 4 weeks later using endoscopy. ***Results.*** After treatment, the Lanza score decreased significantly in group F ($P < 0.001$) but not in group R ($P = 0.478$). The change in the Lanza score in group F was significantly greater ($P = 0.002$) than that in group R. ***Conclusions.*** Famotidine was superior to rebamipide in treating NSAID-associated mucosal lesions.

Key words: famotidine, rebamipide, randomized study, mucosal lesion, NSAID

Introduction

Aspirin, the first nonsteroidal anti-inflammatory drug (NSAID), was synthesized approximately 100 years ago; since then, various NSAIDs have been developed. Owing to their outstanding analgesic actions and relatively high safety levels, NSAIDs are widely used in the treatment of patients who suffer from various forms of chronic pain. Nevertheless, it is well known that NSAID administration, as well as *Helicobacter pylori* infection, are significant causes of gastric mucosal lesions.[1,2]

As the elderly population continues to grow, the number of patients with rheumatoid arthritis, osteoarthritis, osteoporosis, and spondylosis deformans is expected to escalate, with a consequent increase in the frequency of NSAID therapy. In addition, the spread of *H. pylori* eradication therapy is gradually reducing gastric mucosal lesions caused by *H. pylori* infection.[3,4] Consequently, the significance of NSAID-associated gastric mucosal lesions is continuing to increase. The effect of various treatments for these gastric lesions, therefore, requires urgent investigation.

The inhibition of prostaglandin synthesis is believed to be the major mechanism of NSAID-associated gastric mucosal lesions.[5] Other mechanisms, however, are also considered to play a role in NSAID-associated gastric mucosal lesions.[6,7] NSAIDs may cause gastric mucosal lesions by reducing gastric mucosal blood flow.[8] As with other peptic ulcers, the involvement of gastric acid in NSAID-associated gastric mucosal lesions is important.[8] Therefore, acid suppressors are also consid-

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ered effective for NSAID-associated gastric mucosal lesions, as are prostaglandin analogs and other so-called mucoprotective drugs. Indeed, the Guideline for Clinical Practice of Gastric Ulcer Based on EBM (evidence-based medicine) that was developed by a study team from the Ministry of Health, Labour and Welfare in Japan in April 2003 specified that NSAID-associated gastric ulcers should be initially treated by discontinuing NSAID therapy.[1] However, for patients who cannot discontinue NSAIDs, the guideline recommends the administration of prostaglandin analogs or proton pump inhibitors, which are acid suppressors.[1] Histamine-2 receptor antagonists (H_2RAs) are also acid suppressors similar to proton pump inhibitors, although compared with proton pump inhibitors, evidence demonstrating the effect of H_2RAs on NSAID-associated gastric mucosal lesions appears inadequate. Clinical studies have reported that famotidine, an H_2RA, provides excellent prevention and therapeutic actions for NSAID-associated gastric ulcers at high dosages.[9,10] In addition, basic studies have demonstrated that famotidine is significantly more effective than so-called mucoprotective drugs in the prevention of NSAID-associated gastric mucosal lesions.[11] Despite the existence of such evidence, in addition to the fact that famotidine is the most generally used acid suppressor in Japan, no studies have investigated whether low-dose famotidine is effective for NSAID-associated gastric mucosal lesions among Japanese patients who continue NSAID therapy. This topic would therefore appear to be an important area to examine.

In current Japanese clinical settings, so-called mucoprotective drugs other than prostaglandin analogs are more frequently used for the prevention and treatment of gastric mucosal lesions in patients treated with NSAIDs. The major reasons for using this protocol are that the duration of proton pump inhibitor treatment is restricted in Japan and the use of proton pump inhibitors for treatment of NSAID-associated gastric ulcers is not covered under the Japanese health insurance system. Moreover, there are concerns that compliance with prostaglandin therapy may decrease owing to adverse drug reactions to prostaglandin analogs, such as diarrhoea,[12–14] and difficulties can arise with the use of prostaglandins in women who might be pregnant.[15]

The current study compared the effects of low-dose famotidine (20 mg/day) and the so-called mucoprotective rebamipide in the treatment of gastric mucosal lesions (hemorrhage or erosion) in patients receiving long-term NSAID therapy. To ensure objectivity in the determination of drug efficacy, an external endoscopist, who was not informed as to the type of drug administered or the timing of the endoscopy in relation to the therapy regimen, was asked to evaluate the endoscopy findings.

Because many patients with NSAID-associated gastric mucosal lesions do not have subjective symptoms, endoscopy was performed regardless of symptoms in order to examine the actual state of the gastric mucosa in patients receiving long-term NSAID therapy.

Materials and methods

Study institutions

The study was conducted jointly by gastroenterologists and orthopedic surgeons between May 2004 and July 2005 at the Nara Medical University and at four related medical facilities: Nara Prefectural Nara Hospital, Nara Prefectural Gojo Hospital, Kokuho Central Hospital, and Nishi-Nara Chuo Hospital.

Inclusion criteria

The subjects were outpatients, ranging in age from 20 to 75 years, who had been taking NSAIDs, excluding aspirin, for more than 4 weeks, and required continual NSAID therapy after the study.

Exclusion criteria

The following subjects were excluded from the study: those with a previous history of gastrectomy or vagotomy, those with a history of or complications from malignant tumors within 5 years of enrollment, and those with severe liver or kidney disease, severe heart disease, or blood disease. Subjects who were determined inappropriate for the study were also excluded, including pregnant and nursing patients; patients treated with an H_2RA, proton pump inhibitors, muscarine-1 receptor antagonists (M1RAs), or prostaglandin analogs within 4 weeks of enrollment; patients who had altered their NSAID or disease-modifying antirheumatic drug (DMARD) treatments within 4 weeks of enrollment; and patients who had altered their glucocorticoid hormone treatments (except for external use) within 14 days of enrollment (including those who changed only administration or dosage).

Observance of ethical codes

All institutional review boards of the institutions conducting the study approved the protocol prior to the start of the study, which was conducted in accordance with good clinical practice protocols. Written informed consent was obtained from all enrolled patients.

Study methods

The following demographic factors were investigated in all subjects from whom informed consent was obtained:

Table 1. Modified Lanza score

Score	Findings
0	No hemorrhage or erosion observed
1	One or two hemorrhages or erosions observed in one gastric area
2	Three to five hemorrhages or erosions observed in one gastric area
3	Hemorrhages or erosions observed in two gastric areas Six or more hemorrhages or erosions observed in one gastric area, with the total number not exceeding ten in the entire stomach
4	Hemorrhages or erosions observed in three or more gastric areas Eleven or more hemorrhages or erosions observed widely in the entire stomach
5	Ulcer

disease or pathological condition that required chronic NSAID administration, subjective symptoms, ulcer history, smoking history, alcohol consumption, current medications, and so on. Patients were also asked to undergo laboratory analysis (e.g., levels of aspartate aminotransferase and alanine aminotransferase), urine *H. pylori* antibody analysis, and a routine urine test. Patients then confirmed their consent to participate in the study prior to endoscopy, regardless of subjective symptoms. *Helicobacter pylori* infection was examined by a urine-based enzyme-linked immunosorbent assay (Urineliza; Otsuka Pharmaceutical, Tokyo, Japan).[16,17]

Endoscopic findings were assessed according to the modified Lanza score (Table 1).[18,19] Endoscopy photographs with 16 or more image cuts were sent to the endoscopist (i.e., the endoscopic findings judge), who was outside the institutions that conducted the study. The endoscopic findings judge was not informed as to either the study drug or the dates of the photographs. To eliminate endoscopy inconsistencies between institutions, a standard endoscopic method was discussed and selected prior to the start of the study. To minimize variance in the endoscopy results before and after drug treatment, the same endoscopist used the same type of endoscope to photograph the same region at the same angle for each patient.

Patients with Lanza scores ranging from 1–4 (gastric hemorrhage or erosion) were considered eligible for treatment, while those with Lanza scores of 0 (no gastric mucosal lesion) or 5 (gastric ulcer), in addition to those with either gastritis accompanied by elevated erosion or gastritis with manifested Kammrötung were excluded from the treatment groups. Eligible patients were then dynamically assigned to either the famotidine (group F) or rebamipide (group R) treatment group based on the *H. pylori* antibody analysis results (negative or positive) and Lanza score (≥2 or <2). This assignment was performed to prevent an imbalance between the two groups according to *H. pylori* antibody presence, as this factor is considered to significantly impact both the development of gastric mucosal lesions and the course of treatment, in addition to the severity of the gastric mucosal lesions. Patients in group F were administered 10 mg famotidine (Gaster; Astellas Pharma, Tokyo, Japan) twice daily, and patients in group R received 100 mg rebamipide (Mucosta; Otsuka Pharmaceutical) three times daily. The duration of treatment was 4 weeks with a grace period of 7 days. At the time of enrollment, all other medications, such as so-called mucoprotective drugs, antacids, and over-the-counter (OTC) gastric drugs, were discontinued. During treatment, the administration of so-called mucoprotective drugs, antacids, proton pump inhibitors, H_2RAs, M1RAs, prostaglandin analogs, and OTC gastric drugs was prohibited. Changes in NSAID, DMARD, and glucocorticoid hormone treatment were also prohibited, except for topical NSAIDs and glucocorticoids.

The primary end points were determined according to the Lanza score provided by the endoscopic findings judge. Treatment, as a factor in decreasing the Lanza score in each group, as well as changes in the score before and after administration, were compared between the two groups. Secondary end points were determined by the percentage of patients showing complete healing after treatment. Adverse events in which a causal relationship was observed with the treatment were considered adverse drug reactions.

Statistical analysis

Imbalances in patient demographics between the two groups were analyzed using the χ-squared test for nominal scale data, the Wilcoxon rank-sum test for ordinal scale data, and the *t* test to examine quantitative values. Regarding efficacy, changes in the Lanza score before and after treatment were analyzed using the Wilcoxon signed-ranks test, and changes between treatments were analyzed using the Wilcoxon rank-sum test.

Results

Of the 290 patients who gave written consent to participate in the study, 21 patients withdrew consent before the first endoscopy, seven met the exclusion criteria,

and one died of another disease. Thus, only 261 patients actually underwent endoscopy. Findings of the screening endoscopy were as follows: gastric hemorrhage or erosion in 137 patients (52.5%); gastric ulcer in 20 patients (7.7%); duodenal ulcer in 5 patients (1.9%); and combined gastric and duodenal ulcers in 2 patients (0.8%). No gastric mucosal lesions were found in the remaining 97 patients (37.2%). Three patients (1.1%) were found to have malignant tumors (early stage gastric cancer in two patients and esophageal submucosal cancer in one patient).

Gastric mucosal lesions were found in 54 (74.0%) of 73 patients with subjective symptoms, as well as in 110 (58.5%) of 188 patients without such symptoms. Furthermore, the prevalence of gastric mucosal lesions was 60.2% (100/166) in *H. pylori*-positive patients and 67.4% (64/95) in *H. pylori*-negative patients. The prevalence of combined gastric and duodenal ulcers was 14.5% (24 patients) in *H. pylori*-positive patients but only 3.2% (three patients) in *H. pylori*-negative patients.

Of the 137 patients with gastric hemorrhage or erosion, five had high-grade reflux esophagitis and one had esophageal cancer. These six patients were therefore withdrawn from the study for the treatment of those diseases. Furthermore, one patient was withdrawn for taking a H_2RA and one was withdrawn due to a shortage in the amount of NSAID medication prior to enrollment. Eventually, 129 patients were assigned to treatment groups (66 to group F and 63 to group R). Of the patients assigned to these treatment groups, seven discontinued the study (four in group F and three in group R); five refused to undergo the second endoscopy; one violated the study protocol due to a change in NSAID administration; and one developed adverse drug reactions. Of the patients who underwent endoscopy before and after treatment, ten (five in each group) violated the study protocol; 112 patients (57 in group F and 55 in group R) were ultimately eligible for efficacy evaluation.

Table 2 shows the demographic factors of the patients who were assessed for drug efficacy evaluation. The diseases for which chronic NSAID administration was given were rheumatoid arthritis in 47 patients (42.0%); osteoarthritis in 15 patients (13.4%); and other orthopedic diseases, such as spinal canal stenosis, in 50 patients (44.6%). The *H. pylori* infection test result was positive in 60 patients (53.6%). The most common NSAID used was loxoprofen, which was administered to 40 patients (35.7%), followed by diclofenac, which was administered to 33 patients (29.5%). Other than NSAIDs, DMARDs were administered to 45 patients (40.2%) and oral steroids were administered to 18 patients (16.1%). No significant differences between treatments were found after comparisons of age, sex, ulcer history, personal food preferences, lifestyle, NSAID class, or DMARD or steroid treatment.

Figure 1 shows the Lanza scores for each patient, as determined by the endoscopic findings judge, at both baseline and 4 weeks. The distribution of posttreatment Lanza scores in group F showed improvement, although the posttreatment Lanza scores in group R did not. In the posttreatment endoscopy, gastric ulcer (Lanza score 5) was found in one patient (1.8%) in group F, and in three patients (5.5%) in group R. The median Lanza score at both baseline and 4 weeks in group F was 3.0 (1.0, 3.0), (2.4) [median (quartile 1, quartile 3), (mean)] and 1.0 (0.0, 2.0), (1.3), respectively ($P < 0.001$). On the

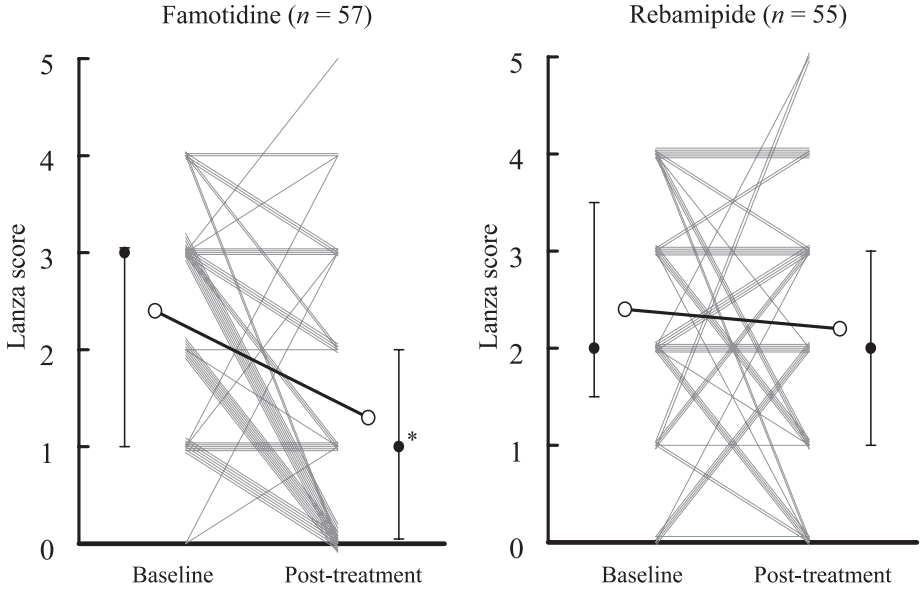

Fig. 1. Change in Lanza score from baseline. ○, mean; ●, median with the first and third quartiles. *$P <$ 0.001; significantly different from the baseline value

Table 2. Patient demographics by treatment

Demographic factor	Treatment		Analysis of imbalance
	Famotidine (n = 57)	Rebamipide (n = 55)	Test result P value
Baseline Lanza score (mean)	2.4	2.4	
Age (years)			0.315
Mean	54.9	57.3	
Range	33–71	20–74	
Duration of disease requiring NSAID administration (months)			0.828
Mean	63.8	67.1	
Range	2–344	1–372	
BMI (kg/m^2)			0.172
Mean	23.7	22.9	
Range	17.1–32.0	14.7–33.6	
No. female patients (%)	41 (71.9)	31 (56.4)	0.128
Diseases requiring NSAID administration, No. of patients (%)			0.398
Rheumatoid arthritis	21 (36.8)	26 (47.3)	
Osteoarthritis	7 (12.3)	8 (14.5)	
Other	29 (50.9)	21 (38.2)	
With subjective gastric symptoms, No. of patients (%)	25 (43.9)	15 (27.3)	0.102
History of peptic ulcer, No. of patients (%)	11 (19.3)	7 (12.7)	0.491
Helicobacter pylori infection, No. of patients (%)	31 (54.4)	29 (52.7)	0.989
Smoking habit, No. of patients (%)	13 (22.8)	12 (21.8)	0.919
Alcohol consumption, No. of patients (%)			0.112
Daily	9 (15.8)	4 (7.3)	
Occasionally	11 (19.3)	19 (34.5)	
Never	37 (64.9)	32 (58.2)	
Coffee consumption, No. of patients (%)	49 (86.0)	46 (83.6)	0.936
Lifestyle, No. of patients (%)			0.856
Keeping regular hours	15 (16.3)	12 (21.8)	
Keeping fairly regular hours	37 (64.9)	38 (69.1)	
Keeping irregular hours	5 (8.8)	5 (9.1)	
NSAIDs[a], No. of patients (%)			
Loxoprofen	22 (38.6)	18 (32.7)	0.652
Diclofenac	19 (33.3)	14 (25.5)	0.480
Meloxicam	5 (8.8)	9 (16.4)	0.353
Lomixicam	3 (5.3)	5 (9.1)	0.675
Other	10 (17.5)	11 (20.0)	
DMARDs, No. of patients (%)	21 (36.8)	24 (43.6)	0.589
Steroids, No. of patients (%)	6 (10.5)	12 (21.8)	0.254

NSAID, nonsteroidal anti-inflammatory drug; BMI, body mass index; DMARDs, disease-modifying antirheumatic drugs
[a] Including redundancy due to combination therapy: two combination therapies in group F (loxoprofen + acemetacin, diclofenac + diclofenac supposiitory); two combination therapies in group R (diclofenac + zaltoprofen, loxoprofen + meloxicam)

other hand, the median Lanza score at both baseline and 4 weeks in group R was 2.0 (1.5, 3.5), (2.4) and 2.0 (1.0, 3.0), (2.2), respectively. Thus, no significant differences were found in Lanza scores after treatment with rebamipide (P = 0.478). The median change in the Lanza score between baseline and 4 weeks of treatment was –1.0 (–2.0, 0.0), (–1.2) in group F and 0.0 (–2.0, 1.0), (–0.2) in group R (P = 0.002). In addition, the percentage of patients that showed complete healing after treatment in group F was 45.6% (26/57) and 18.2% (10/55) in group R.

Figure 2 shows the median change in Lanza score from baseline in relation to both *H. pylori* infection and treatment. The median Lanza score significantly changed from 3.0 (2.0, 3.0), (2.6) to 1.0 (0.0, 3.0), (1.5) without *H. pylori* (P < 0.001) and from 3.0 (1.0, 3.0), (2.3) to 1.0 (0.0, 2.0), (1.1) with *H. pylori* (P = 0.004) after famotidine treatment. On the other hand, the median Lanza score changed from 3.0 (2.0, 4.0), (2.7) to 3.0 (1.0, 3.0), (2.2) without *H. pylori* (P = 0.133) and from 2.0 (1.0, 3.0), (2.1) to 2.0 (1.0, 3.0), (2.2) with *H. pylori* (P = 0.573) after rebamipide treatment.

Adverse drug reactions were observed in all 129 patients who were treated. The occurrence of adverse drug reactions in group F was 15.2% (10/66); the main adverse drug reactions were increased alanine aminotransferase levels (2/66) and increased blood urea nitrogen (2/66). In group R, adverse drug reactions were

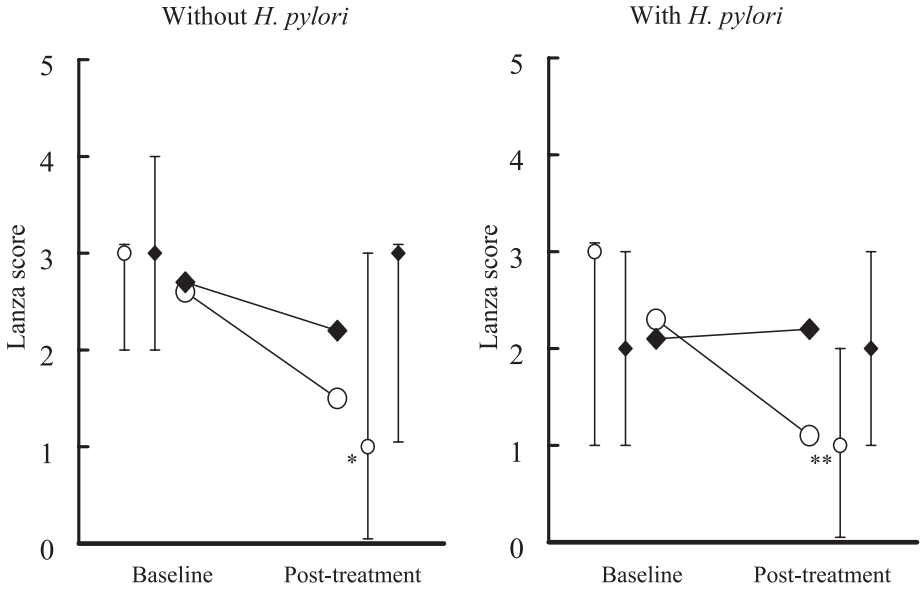

Fig. 2. Median and mean change in Lanza score from baseline in relation to *Helicobacter pylori* infection and treatment. ○, famotidine (without *H. pylori*; $n = 26$, with *H. pylori*; $n = 31$); ◆, rebamipide (without *H. pylori*; $n = 26$, with *H. pylori*: $n = 29$). *Large symbol*, mean; *small symbol*, median with the first and third quartiles. $*P = 0.001$, $**P = 0.004$; significantly different from the baseline value

observed in 15.9% (10/63) of patients; the main adverse drug reactions were increased aspartate aminotransferase levels (2/63), increased blood urea nitrogen (2/63), and increased white blood cell count (2/63). One patient in group R withdrew from the study because of constipation, thirst, and headache during therapy, although no serious adverse reaction was observed.

Discussion

Many studies have demonstrated that acid suppressors are useful in the treatment of NSAID-associated gastric mucosal lesions, suggesting that gastric acid acts as a noxious ulcerogenic agent.[9,20,21] The main acid suppressors currently used are proton pump inhibitors and H_2RAs, for which there is a general consensus on their usefulness. A study using experimental animals indicated that famotidine is more effective for the control of NSAID-associated gastric mucosal lesions than so-called mucoprotective drugs.[11] Clinical studies have failed to show that these so-called mucoprotective drugs prevent NSAID-associated ulcers in patients receiving long-term NSAID therapy for rheumatoid arthritis. Although several studies have reported the ulcer-preventative effects of famotidine,[22] only Taha et al.[9] conducted a randomized controlled study that focused on the effects of H_2RAs, reporting that high-dose famotidine treatment is effective for preventing and treating NSAID-associated gastric ulcers. In Japan, health insurance policy restrictions make it difficult to prescribe proton pump inhibitors for long-term treatment of NSAID-associated gastric mucosal lesions. Thus, there are high expectations regarding the therapeutic and preventative effects of H_2RAs on NSAID-associated gastric mucosal lesions.

Although famotidine is an effective treatment of NSAID-associated gastric mucosal lesions, previous results in the literature were based on studies carried out in Europe. In these studies, the dosage of famotidine used was 2–4 times the dosages used in Japanese clinical settings. The present study examined the efficacy of famotidine in the treatment of NSAID-associated gastric mucosal lesions using the dosage used in general Japanese clinical settings and comparing this with cytoprotective levels of rebamipide. Rebamipide was selected as the control drug in this study as it is ethically difficult to use placebo as a control, given that NSAIDs are clearly known to cause gastric mucosal lesions. In addition, most general physicians in Japan prefer to use cytoprotective therapy rather than prostaglandin analogs for the prevention and treatment of gastric mucosal lesions caused by the use of NSAIDs. Rebamipide is considered to be capable of preventing gastric mucosal lesions during short-term NSAID therapy[19] and has recognized efficacy in the treatment of NSAID-associated gastric mucosal lesions (hemorrhage/erosion).[23,24] The dosage of famotidine was set at 20 mg/day because the approved dosage of famotidine for gastric mucosal lesions (hemorrhage/erosion) in Japan is 20 mg/day.

Our study indicated that, compared with rebamipide (300 mg/day), famotidine (20 mg/day) provided significantly better treatment of gastric mucosal lesions (hemorrhage/erosion) in patients receiving long-term NSAID therapy (Figs. 1 and 2). For the purposes of this study, it is important that the results of treatment were obtained under continual NSAID administration. So-called mucoprotective drugs and H_2RAs have been

reported to have positive effects on the treatment of gastric mucosal lesions when NSAIDs are discontinued. However, these positive effects are reduced when NSAID therapy is continued.[9,10] Many patients who receive long-term NSAID therapy have difficulty discontinuing these drugs, making therapeutic performance during ongoing NSAID therapy more important.

Unlike in Western studies,[9] low-dose famotidine (20 mg/day) is likely to be effective because sufficient acid-suppressing effects can be attained with a low-dose regimen. These effects may be due to the physical characteristics of the Japanese, who have lower acid secretions than do Caucasians and other races in Western nations.[25–27] One reason for this low-acid secretion is the high prevalence of *H. pylori* infection in Japan. Unlike Caucasians, many Japanese with *H. pylori* infection develop severe gastric mucosal lesions.[28,29] Indeed, in the present study, half of the patients were *H. pylori*-positive (Table 2).

In the present study, endoscopy was performed on patients receiving chronic NSAID administration, regardless of symptoms. Therefore, the data on the prevalence of gastric mucosal lesions obtained in this study should be considered reliable. Gastric mucosal lesions were observed in more than half of the patients without subjective symptoms, confirming that subjective symptoms cannot be considered a sensitive predictor of gastric mucosal lesions in patients who receive long-term NSAID therapy,[22] as previously reported. It was also important to involve an outside endoscopist in order to ensure the fairness, objectivity, and reproducibility of the results presented in this study.

In conclusion, the results presented here recommend 20 mg/day famotidine for the treatment of NSAID-associated gastric mucosal lesions.

References

1. Research Team for the Development of Guidelines for Evidence-Based Gastric Ulcer Diagnosis, Guideline for Clinical Practice of Gastric Ulcer Based on EBM (in Japanese with English abstract). Jiho 2003;7–14.
2. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet 2002;359:14–22.
3. Asaka M, Satoh K, Sugano K, Sugiyama T, Takahashi S, Shimoyama T, et al. Guidelines in the management of *Helicobacter pylori* infection In Japan. Helicobacter 2001;6:177–86.
4. Miwa H, Sakaki N, Sugano K, Sekine H, Higucni K, Sugiyama T, et al. Recurrent peptic ulcers in patients following successful *Helicobacter pylori* eradication: a multicenter study of 4940 patients. Helicobacter 2004;9:9–26.
5. Robert A. Antisecretory anti-ulcer, cytoprotective and diarrheogenic properties of prostaglandins. Adv Prostaglandin Thromboxane Res 1976;2:507–20.
6. Ligumsky M, Golanska EM, Hansen DG, Kauffman GL. Aspirin can inhibit gastric mucosal cyclo-oxygenase without causing lesions in rat. Gastroenterology 1983;84:756–61.
7. Frezza M, Gorji N, Melato M. The histopathology of non-steroidal anti-inflammatory drug induced gastroduodenal damage: correlation with *Helicobacter pylori*, ulcers, and hemorrhagic events. J Clin Pathol 2001;54:521–5.
8. Funatsu T, Chono K, Hirata T, Keto Y, Kimoto A, Sasamata M. The possible role of gastric acid against non-steroidal anti-inflammatory drugs-induced gastric microcirculatory disturbance in rats. Jpn Pharmacol Ther 2004;32:429–34.
9. Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye PE, Cottrell J, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med 1996;334:1435–9.
10. Hudson N, Taha AS, Russell RI, Trye P, Cottrell J, Mann SG, et al. Famotidine for healing and maintenance in nonsteroidal anti-inflammatory drug-associated gastroduodenal ulceration. Gastroenterology 1997;112:1817–22.
11. Keto Y, Funatsu T, Hirata T, Toyama T, Sudoh K, Sasamata M. Inhibitory effects of famotidine on NSAIDs and bisphosphonate-induced mucosal lesions in rats. Jpn Pharmacol Ther 2003;31:485–93.
12. Raskin JB, White RH, Jackson JE, Weaver AL, Tindall EA, Leis RB, et al. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens. Ann Intern Med 1991;115:195–200.
13. Agrawal NM, Van Kerckhove HE, Erhardt LJ, Geis GS. Misoprostol coadministered with diclofenac for prevention of gastroduodenal ulcers. A one-year study. Dig Dis Sci 1995;40:1125–31.
14. Bocanegra TS, Weaver AL, Tindall EA,Sikes DH, Ball JA, Wallemark CB, et al. Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial. Arthrotec Osteoarthritis Study Group. J Rheumatol 1998;25:1602–11.
15. Walt RP. Misoprostol for the treatment of peptic ulcer and antiinflammatory-drug-induced gastroduodenal ulceration. N Engl J Med 1992;327:1575–80.
16. Katsuragi K, Noda A, Tachikawa T, Azuma A, Mukai F, Murakami K, et al. Highly sensitive urine-based enzyme-linked immunosorbent assay for detection of antibody to *Helicobacter pylori*. Helicobacter 1998;3:289–95.
17. Kato M, Asaka M, Saito M, Sekine H, Ohara S, Toyota T, et al. Clinical usefulness of urine-based enzyme-linked immunosorbent assay for detection of antibody to *Helicobacter pylori*: a collaborative study in nine medical institutions in Japan. Helicobacter 2000;5:109–19.
18. Lanza FL, Royer GL, Nelson RS, Chen TT, Seckman CE, Rack MF. A comparative endoscopic evaluation of the damaging effects of nonsteroidal anti-inflammatory agents on the gastric and duodenal mucosa. Am J Gastroenterol 1981;75:17–21.
19. Naito Y, Yoshikawa T, Iinuma S, Yagi N, Matsuyama K, Boku Y, et al. Rebamipide protects against indomethacin-induced mucosal lesion in healthy volunteers in a double-blind, placebo-controlled study. Dig Dis Sci 1998;43:83–9.
20. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998;338:727–34.
21. Wu CS, Wang SH, Chen PC, Wu VCC. Dose famotidine have similar efficacy to misoprostol in the treatment of non-steroidal anti-inflammatory drug-induced gastropathy? Int J Clin Pract 1998;52:472–4.
22. Miyake K, Ueki N, Suzuki K, Shinji Y, Kusunoki M, Hiratsuka T, et al. Preventive therapy for non-steroidal anti-inflammatory drug-induced ulcers in Japanese patients with rheumatoid arthritis: the current situation and a prospective controlled-study of

the preventive effects of lansoprazole or famotidine. Aliment Pharmacol Ther 2005;21(Suppl 2):67–72.
23. Kitagami K, Oku K, Umemoto N,Mizokami Y, Shiozama K, Yamana S, et al. Clinical study of rebamipide for NSAIDs induced gastritis. J Adult Dis 1993;23:1477–88.
24. Matsuhisa T, Hayama T, Nakamura H, Yoshino S, Yamada N. Clinical usefulness of rebamipide against symptoms, gastric lesions and histological gastritis caused by long-term administration of NSAIDs in patients with rheumatoid arthritis. Gastroenterology (Tokyo) 1998;27:118–30.
25. Kinoshita Y, Kawanami C, Kishi K, Nakata H, Seino Y, Chiba T. *Helicobacter pylori* independent chronological change in gastric acid secretion in the Japanese. Gut 1997;41:452–8.
26. El-Omar EM, Penman ID, Ardill JES, Chittajallu RS, Howie C, Mccoll KEL. *Helicobacter pylori* infection and abnormalities of acid secretion in patients with duodenal ulcer disease. Gastroenterology 1995;109:681–91.
27. Feldman M, Richardson CT, Lam SK, Samloff IM. Comparison of gastric acid secretion rates and serum pepsinogen I and II concentrations in occidental and oriental duodenal ulcer patients. Gastroenterology 1988;95:630–5.
28. Kawaguchi H, Haruma K, Komoto K, Yoshihara M, Sumii K, Kajiyama G. *Helicobacter pylori* infection is the major risk factor for atrophic gastritis. Am J Gastroenterol 1996;91:959–62.
29. Haruma K, Kamada T, Kawaguchi H, Okamoto S, Yoshihara M, Sumii K, et al. Effect of age and *Helicobacter pylori* infection on gastric acid secretion. J Gastroenterol Hepatol 2000;15:277–83.