

## Original article

# Up-to-date information on gastric mucosal lesions from long-term NSAID therapy in orthopedic outpatients: a study using logistic regression analysis

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### Abstract

**Background.** An increase in gastric mucosal lesions due to nonsteroidal antiinflammatory drugs (NSAIDs) has been reported along with the aging of society; even orthopedic surgeons can no longer remain unconcerned about this disease. However, no study has accurately examined the incidence of gastric mucosal lesions; therefore, adequate evidence has not been established. In this study, endoscopic examinations were performed to determine the status of gastric mucosal lesions in patients receiving long-term NSAID therapy.

**Methods.** In 261 patients receiving NSAIDs other than aspirin for more than 28 days, excluding external application, upper gastrointestinal endoscopy was performed regardless of any subjective symptoms after obtaining the patient's medical history. The severity of the gastric mucosal lesions was evaluated using the modified Lanza score. Patient factors involved in the development of lesions were examined using a logistic regression analysis with criterion variables of gastric mucosal lesions and ulcers and the factors of sex, age, *Helicobacter pylori* infection, and type of NSAID as candidates for the explanatory variable.

**Results.** Gastric mucosal lesions were observed in 164 patients (62.8%); 27 (10.3%) had ulcers. The use of diclofenac, subjective symptoms, irregular lifestyle, and increased body mass index (BMI) were four factors associated with the development of gastric mucosal lesions; the odds ratios were 2.99, 1.92, 1.80, and 1.09, respectively. Also, the use of diclofenac, presence of *H. pylori*, irregular lifestyle, alcohol consumption, and aging were five factors associated with the development of ulcers; the odds ratios were 6.40, 6.07, 2.62, 2.06, and 1.05, respectively.

**Conclusions.** Diclofenac can cause gastric mucosal lesions, including ulcers, more easily than other NSAIDs. *H. pylori* infection is a high-risk factor for ulcers in patients receiving long-term NSAIDs therapy. In NSAID-treated patients, subjective symptoms are not grounds for a diagnosis of gastric mucosal lesions, especially ulcers.

### Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) have a long history. Aspirin was synthesized as the first NSAID a century ago, and since then several types of NSAID have been developed. NSAIDs have excellent analgesic action with high safety; therefore, they are used to treat pain with many diseases. In the area of orthopedics, long-term NSAID therapy is prescribed not only for patients with acute conditions, such as trauma, but also for the treatment of chronic diseases, such as arthropathies, including rheumatoid arthritis and low back pain. However, gastric mucosal lesions have long been identified as a side effect of NSAIDs.<sup>1</sup> Many orthopedists recognize the side effect but do not attach great importance to it. In the United States, however, it is estimated that 100 000 or more people are admitted to the hospital because of gastric mucosal lesions due to NSAIDs, with 15 000 or more cases resulting in mortality.<sup>2</sup> In a future, rapidly aging society, the number of patients with such diseases as osteoarthritis, spondylosis deformans, and osteoporosis can be expected to increase, leading to an accelerated increase in the use of NSAIDs. Therefore, the significance of NSAIDs-induced gastric mucosal lesions will increase, and understanding the actual state of NSAIDs-induced gastric mucosal lesions will be clinically critical.

Shiokawa et al. described a study of 1008 patients receiving long-term NSAID therapy who underwent upper gastrointestinal (GI) endoscopy for gastric mucosal lesions.<sup>3</sup> Overall, lesions were observed in 627 patients (62.2%), including gastric ulcers in 156 patients (15.5%) and gastritis in 388 patients (38.5%), indicating that the incidence of gastric mucosal lesions was high in patients receiving NSAID therapy. However, there have been few investigations of this issue in Japan. In particular, there are many uncertainties about the actual state of gastric mucosal lesions due to NSAIDs, which have been used widely in recent years.

Under these circumstances, we compared the therapeutic effects of famotidine and rebamipide for gastric mucosal lesions (bleeding and erosion) in patients receiving long-term NSAID therapy (FORCE study).<sup>4</sup> In this study, the development of gastric mucosal lesions was examined in detail in patients receiving long-term NSAID therapy based on the results of upper GI endoscopy for screening prior to this study.

## Materials and method

A multicenter study was conducted from May 2004 to July 2005 by gastroenterologists and orthopedists from the Nara Medical University and its four associated institutions: Nara Prefectural Nara Hospital, Nara Prefectural Gojo Hospital, Kokuho Central Hospital, and Nishi Nara Chuo Hospital. The protocol was approved by the institutional review boards of all participating institutions. The study was conducted in compliance with good clinical practices, and written informed consent was obtained from all study participants.

### Materials

Subjects were outpatients with ages ranging between 20 and 74 years who were receiving any NSAID other than aspirin, excluding external application, for more than 4 weeks. Patients receiving any agent, including histamine receptor antagonists, proton pump inhibitors, muscarinic receptor antagonists, and prostaglandins within 4 weeks before the endoscopy were excluded. Additionally, patients were excluded if any change in regimen, including dosage and administration, of NSAIDs or disease-modifying antirheumatic drugs (DMARDs) occurred within 4 weeks before the endoscopy. In addition, patients were excluded if there was any change in the regimen of adrenocortical hormones, excluding external application, within 14 days before the endoscopy.

### Method

After a complete medical history was obtained from patients who gave consent, a urinary anti-*H. pylori* antibody test (enzyme-linked immunosorbent assay) was performed followed by endoscopy regardless of subjective symptoms. A modified Lanza score (referred to as a Lanza score),<sup>5</sup> a scoring system reported by Lanza,<sup>6</sup> was used for evaluation of endoscopic findings.

### Investigations and statistical analyses

The development of gastric mucosal lesions was tabulated on the basis of the Lanza score according to endo-

scopic findings. Then patient factors involved in the development of lesions were tested using a logistic regression analysis where gastric mucosal lesions (Lanza score 0 or 1–5) and ulcers (Lanza score 0–4 or 5) were criterion variables, and sex and age, presence of *H. pylori* infection, type of NSAID, and subjective symptoms were candidates for explanatory variables. “Lifestyle,” one of the candidate explanatory variables, was subjectively self-assessed by subjects in interview surveys. They were asked to assess their daily life pattern (e.g., bedtime, hour of rising, and mealtimes) in three grades: regular, almost regular, and irregular. In the logistic regression, in a stepwise manner, the odds ratio and 95% confidence interval (95% CI) were calculated for selected explanatory variables according to the inclusion criteria for the explanatory variable as  $P < 0.1$ . The  $P$  value was calculated using the Wald test, and  $P < 0.05$  was considered statistically significant.

## Results

### Patients' medical history

Consent was obtained from 290 patients. Among them, 21 patients withdrew consent before the endoscopy, 7 met the exclusion criterion, and 1 died of other causes; therefore, 261 patients underwent endoscopy. Their medical histories are shown in Table 1, according to the factors used as candidates for explanatory variables in the logistic regression analysis.

Patients ranged in age from 20 to 74 years (mean 58.2 years) with a mean body mass index (BMI) of 23.0 kg/m<sup>2</sup>. Underlying diseases included rheumatoid arthritis in 100 patients (38.3%), osteoarthritis in 37 patients (14.2%), and other diseases in 124 patients (47.5%). A history of ulcers was noted in 42 patients (16.1%), and the anti-*H. pylori* antibody test before endoscopy revealed that 166 patients (63.6%) were positive.

The details of administered NSAIDs and combined mucosal protective agents and DMARDs, including duplication due to combination, are described as follows: Among the NSAIDs, 94 patients (36.0%) received loxoprofen, 36 (13.8%) received diclofenac, 34 (13.0%) received sustained-release diclofenac capsule (diclofenac SR), 42 (16.1%) received a preferential cyclooxygenase-2 (COX-2 inhibitor; meloxicam or etodolac), and 64 (24.5%) received others. Mucosal protective agents, mainly teprenone in 103 (39.5%) and rebamipide in 74 (28.4%), were administered in combination with others in 250 of 261 (95.8%) patients. DMARDs were administered in 93 patients (35.6%) in combination with others, including bucilamine in 54 (20.7%) and methotrexate in 45 (17.2%).

### Details of gastric mucosal lesions

Altogether, 164 (62.8%) patients had gastric mucosal lesions, of which ulcers (Lanza score 5) were observed in 27 (10.3%) and bleeding and erosion (Lanza score 1–4) in 137 (52.5%). The Lanza score was 1 in 26 (10.0%), 2 in 23 (8.8%), 3 in 59 (22.6%), and 4 in 29 (11.1%). There were only 97 patients (37.2%) with no lesions (Lanza score 0).

The frequency of gastric mucosal lesions for each type of NSAID was as follows: 83.3% (30/36) in patients receiving diclofenac, 73.5% (25/34) in those receiving diclofenac SR, 58.5% (55/94) in those receiving loxoprofen, and 54.8% (23/42) in those receiving a preferential COX-2 inhibitor. When the subjects were divided according to the presence of *H. pylori* infection, the incidence 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 incidence of ulcers was 14.5% (24/166) in *H. pylori*-positive patients and only 3.2% (3/95) in *H. pylori*-negative patients. When the incidence of gastric mucosal lesions with or without subjective symptoms was examined, 74.0% (54/73) of patients with subjective symptoms had gastric mucosal lesions, and 58.5% (110/188) of those without subjective symptoms had gastric mucosal lesions.

The incidence of gastric mucosal lesions was 60.9% (53/87) in those aged  $\geq 65$  years and 63.8% (111/174) in those  $< 65$  years. When patients were stratified into short- or long-term NSAID therapy, the incidence was 72.2% (39/54) for those receiving therapy for 1–3 months and 60.4% (125/207) for those receiving therapy for  $\geq 3$  months.

### Results of logistic regression analysis

The following are the results of the logistic regression analysis where the criterion variables were gastric mucosal lesions and ulcers, and the factors in the medical history shown in Table 1 were candidates for explanatory variables. Patient factors involved in the pathogenesis of gastric mucosal lesions included the use of diclofenac, history of ulcers, subjective symptoms, timing of the initiation of NSAIDs, lifestyle, dosage of NSAIDs, and BMI, of which the use of diclofenac, subjective symptoms, lifestyle, and BMI were significant (Fig. 1). The odds ratios (95% CI) of the four factors were 2.99 (1.15–7.77) ( $P = 0.025$ ) between patients taking diclofenac and those who did not, 1.92 (1.00–3.66) ( $P = 0.049$ ) between those with and without subjective symptoms, 1.80 (1.15–2.81) ( $P = 0.011$ ) among 1° differences in irregularity of lifestyle, and 1.09 (1.00–1.19) ( $P = 0.040$ ) among 1 kg/m<sup>2</sup> differences in BMI.

Patient factors involved in the pathogenesis of ulcers included the use of diclofenac, *H. pylori* infection, use

**Table 1.** Patients' medical histories ( $n = 261$ , candidates for explanatory variable for logistic regression analysis)

Factors in medical history	No.	%
Sex		
Female	171	65.5
Underlying diseases		
Rheumatoid arthritis	100	38.3
Osteoarthritis	37	14.2
Others	124	47.5
Anti- <i>H. pylori</i> antibody		
Positive	166	63.6
Peptic ulcer history		
Yes	42	16.1
Subjective symptoms		
Yes	73	28.0
Smoking habit		
Yes	62	23.8
Alcohol habit <sup>a</sup>		
No	162	62.1
Occasionally	69	26.4
Daily	30	11.5
Coffee habit		
Yes	216	82.8
Lifestyle <sup>a</sup>		
Regular	82	31.4
Almost regular	152	58.2
Irregular	26	10.0
Unknown	1	0.4
Particular stress		
Yes	57	21.8
Unknown	2	0.8
Type of NSAIDs <sup>b</sup>		
Loxoprofen	94	36.0
Preferential COX-2 inhibitor <sup>c</sup>	42	16.1
Diclofenac	36	13.8
Diclofenac SR	34	13.0
Others	64	24.5
NSAIDs administration		
1–3 months	54	20.7
> 3 months	207	79.3
Dosage of NSAIDs <sup>a</sup>		
Below usual dose	68	26.1
Usual dose	169	64.8
Double or combination <sup>d</sup>	24	9.2
Type of mucosal protective agents <sup>b</sup>		
Teprenone	103	39.5
Rebamipide	74	28.4
Type of DMARDs <sup>b</sup>		
Bucilamine	54	20.7
Methotrexate	45	17.2
Bisphosphonate		
Yes	17	6.5
Steroids		
Yes	49	18.8

The mean and range of all patients' ages are 58.2 years and 20.0–74.0 years, respectively; the mean and range of all patients' BMI (kg/m<sup>2</sup>) are 23.0 and 14.7–33.6, respectively

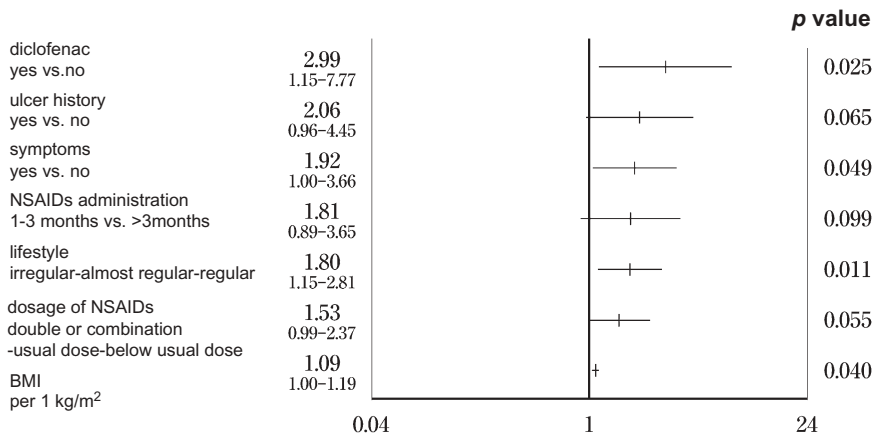
NSAIDs, nonsteroidal antiinflammatory drugs; DMARDs, disease-modifying antirheumatic drugs

<sup>a</sup>Factors used as continuous variables in multi-logistic regression analysis. (The rest are discrete variables)

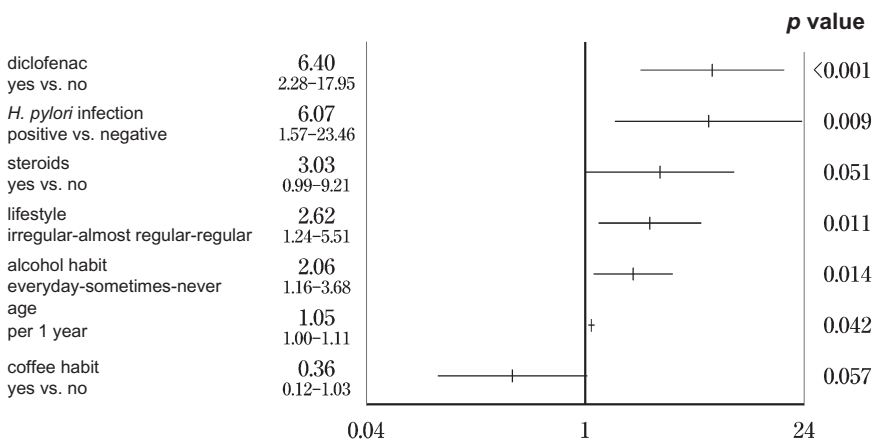
<sup>b</sup>Including duplication due to combination

<sup>c</sup>Meloxicam ( $n = 34$ ) + Etodolac ( $n = 8$ )

<sup>d</sup>Combination between NSAIDs including aspirin



**Fig. 1.** Patient factors involved in the pathogenesis of gastric mucosal lesions



**Fig. 2.** Patient factors involved in the pathogenesis of ulcers

of steroid, lifestyle, alcohol consumption, age, and coffee consumption, of which a significant association was confirmed in the use of diclofenac, *H. pylori* infection, lifestyle, alcohol consumption, and age (Fig. 2). The odds ratios (95% CI) of the five factors were 6.40 (2.28–17.95) ( $P < 0.001$ ) between patients taking/not taking diclofenac, 6.07 (1.57–23.46) ( $P = 0.009$ ) between positive and negative for *H. pylori* infection, 2.62 (1.24–5.51) ( $P = 0.011$ ) among 1<sup>o</sup> differences in irregularity of lifestyle, 2.06 (1.16–3.68) ( $P = 0.014$ ) among 1<sup>o</sup> differences in the frequency of alcohol consumption, and 1.05 (1.00–1.11) ( $P = 0.042$ ) among 1 year differences in age.

## Discussion

NSAIDs may injure the gastric and duodenal mucosa, given the pharmacological mechanism of inhibition of prostaglandin synthesis,<sup>7</sup> which could be confirmed through endoscopy. In Japan, Shiokawa et al. reported that the incidence of ulcers was approximately 15%.<sup>3</sup> NSAIDs have been partly devised in the area of the

drug delivery system (DDS) in their history of development, and most orthopedists presume that gastric mucosal lesions due to NSAIDs may be clinically less important if mucosal protective agents are administered concomitantly.

In this epidemiological study, mucosal protective agents were concomitantly administered in 250 (95.8%) of the 261 patients. Despite this, surprisingly, gastric mucosal lesions were observed in 62.8% of patients. Although no study using the Lanza score has been conducted in Japan on the incidence of gastric mucosal lesions in healthy individuals, the Japanese Society of Gastroenterological Cancer Screening reported that the incidence of gastric ulcers was 1.04%<sup>8</sup> (Lanza score grade 5). Comparison between this figure and the one obtained in this study (10.3%) implies that the incidence of gastric ulcers is higher in patients receiving NSAIDs. Therefore, orthopedists should recognize the importance of gastric mucosal lesions due to NSAIDs, especially in patients receiving long-term NSAID therapy, and pay close attention to lesions.

*H. pylori* infection is one of the two major risk factors for an ulcer, along with NSAIDs.<sup>9,10</sup> As indicated in this



study, NSAIDs are an independent risk factor for gastric mucosal lesions regardless of *H. pylori* infection; that is, patients receiving NSAIDs are always at risk for gastric mucosal lesions regardless of their medical history.

On the other hand, there is no definite correlation between NSAIDs and *H. pylori* infection in the development of peptic ulcers. In this study, *H. pylori* infection was considered a risk factor for peptic ulcers in patients receiving NSAIDs, whereas gastric mucosal lesions were not. The results may be interpreted as NSAIDs having a significant influence on the gastric mucosa sufficient to mask the influence of *H. pylori* infection rather than *H. pylori* infection inhibiting the increased risk of gastric mucosal lesions due to NSAIDs. However, it would be rash to conclude that NSAIDs are a more important risk factor for gastric mucosal lesions than *H. pylori* infection based only on the results of this study; further investigations are needed.

The result that *H. pylori* infection is a risk factor for peptic ulcers in patients receiving NSAIDs is consistent with the results by Chan et al.<sup>11</sup> The detailed mechanisms by which *H. pylori* infection increases peptic ulcer risks in patients receiving NSAIDs are not fully understood. However, it is likely that vulnerable mucosa with chronic inflammation caused by *H. pylori* infection is more susceptible to NSAIDs, injurious substances, than healthy mucosa. It has been suggested that, in addition to NH<sub>3</sub> and other injurious substances produced by *H. pylori*, inflammatory cell infiltration as a response to bacterial infection and the associated cytokines and free radicals are involved in the mechanisms of gastric mucosal lesions caused by *H. pylori* infection.<sup>12</sup> It is likely that the incidence of peptic ulcers increases when NSAIDs, which are prostaglandin inhibitors<sup>13</sup> and directly injurious,<sup>14</sup> are administered to patients with gastric mucosa affected by various injurious factors caused by *H. pylori* infection. Furthermore, delayed healing of ulcers was reported in patients who took acid-suppressant drugs while continuing to take NSAIDs.<sup>15</sup> Thus, administration of NSAIDs certainly has harmful effects on patients with peptic ulcers. As described above, and although no conclusions can be drawn, the results of the study can serve as a warning about drug selection for patients with *H. pylori* infection.

The risk of gastric mucosal lesions in patients with subjective symptoms increased less than twice, showing that subjective symptoms were not a significant risk factor for peptic ulcers. Indeed, the prevalence of gastric mucosal lesions reached 58.5% in patients without subjective symptoms, where 10.1% had peptic ulcers. This means that in patients receiving NSAIDs subjective symptoms are not a basis for the diagnosis of gastric mucosal lesions, especially peptic ulcers. This supports

previous reports that many gastric mucosal lesions due to NSAIDs are asymptomatic.<sup>3,16,17</sup>

In this study, lifestyle was selected as one of the risk factors for gastric mucosal lesions including peptic ulcers. Although lifestyle was based on the subjective opinions of patients without an objective evaluation, lifestyle was suggested as a possible risk factor for gastric mucosal lesions if a patient considered his or her lifestyle irregular. There have been reports that irregular lifestyle, which cannot be an independent risk factor for peptic ulcer, can cause not only peptic ulcers but also severe consequences, such as hematemesis, when other risk factors, such as *H. pylori* infection, are added,<sup>18</sup> suggesting that exercising caution in terms of lifestyle habits, such as alcohol ingestion and smoking, for patients receiving NSAIDs, may be worthwhile.

As another risk factor for gastric mucosal lesions, including peptic ulcers, diclofenac, which is generally considered to have a potent antiinflammatory analgesic effect, was selected. Diclofenac is conventionally known to provide a higher risk of upper GI hemorrhage than any other NSAIDs<sup>19</sup>; therefore, close attention should be paid to its use while a superior analgesic effect is expected. Although the results of this study cannot demonstrate whether there are differences in risks for gastric mucosal lesions among the NSAIDs other than diclofenac, conventional NSAIDs including loxoprofen, meloxicam, and etodolac, which are considered preferential COX-2 inhibitors and cause fewer gastric mucosal lesions, could unexpectedly cause gastric mucosal lesions in more than half of patients. Because NSAIDs such as meloxicam and etodolac are not designed to target COX-2, they are not true COX-2 selective inhibitors. No significant difference was reported between meloxicam and piroxicam, a conventional NSAID, in terms of the incidence of gastric mucosal lesions in a study in which patients were endoscopically examined after meloxicam (15 mg/day, a dosage approved in Japan) or piroxicam (20 mg/day) was administered for 1 month.<sup>20</sup> Therefore, studies must be conducted in patients receiving COX-2 selective inhibitors, such as celecoxib, before the association between COX-2 selective inhibitors and gastric mucosal lesions is determined in Japan.

Within the scope of this study, there was no increase in the risk for gastric mucosal lesions, which depended on the period of NSAIDs therapy. This was partly because of the suggestion that, once developed, gastric mucosal lesions may possibly be repaired through the administration of NSAIDs for several weeks because of adaptation.<sup>21,22</sup> However, it was reported that a longer period, as well as a larger dose, of NSAIDs therapy could cause an increase in the incidence,<sup>23</sup> suggesting that monitoring with periodic endoscopy and blood examinations would be needed in patients requiring long-term NSAIDs therapy.

The incidence of gastric mucosal lesions in patients receiving NSAIDs demonstrated in this study was similar to that reported by Shiokawa et al.<sup>3</sup> even though the patients' medical history was slightly different. During the past decade, it is notable that these results were obtained despite the fact that NSAIDs have been developed and improved. Under the current circumstances, many patients receiving NSAIDs have a high possibility of developing gastric mucosal lesions. In any case, gastric mucosal lesions are often asymptomatic in patients receiving NSAIDs; therefore, orthopedists should control pain with NSAIDs with a keen recognition that greater awareness of the risk of gastric mucosal lesions and measures for them are essential even if there are no complaints.

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