Prescription of Nonsteroidal Anti-inflammatory Drugs and Co-prescribed Drugs for Mucosal Protection: Analysis of the Present Status Based on Questionnaires Obtained from Orthopedists in Japan

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Abstract

Objective Recently guidelines for the treatment and prevention of ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs) have been established. The aim of the present study was to examine factors influencing orthopedists in Japan in the use of cytoprotective drugs to prevent NSAID-associated gastrointestinal adverse events.

Methods We sent a questionnaire to 402 orthopedists in Hyogo Prefecture. A standardized 10-item questionnaire was used to collect information on NSAID prescriptions (drug name, pharmaceutical form, doses, and duration of use) and associated drugs, especially gastroprotective drugs.

Results Two hundred eight (51.7%) orthopedists returned the questionnaire. The most frequently used NSAIDs, in descending order, were loxoprofen sodium, diclofenac sodium, and etodolac. Most doctors (80%) reported patients with abdominal symptoms associated with NSAIDs. Of these doctors, 59% treated the symptoms by themselves, and prescribed gastroprotective agents (32.2%), histamine H₂-receptor antagonists (H₂RAs) (26.4%), prostaglandin analogues (PAs) (17.0%), or proton pump inhibitors (PPIs) (16.2%). Sixty-seven percent of doctors reported that those drugs reduced the symptoms. Most orthopedists (96%) prescribed some type of drug to prevent NSAID-associated gastrointestinal events, including gastroprotective drugs (44.6%), H₂RAs (19.5%), PAs (17.4%), and PPIs (10.8%). The doctors reported that they prescribed medicines for NSAID-associated gastrointestinal events on the basis of their experience (23%), by considering medical insurance restrictions (17%), and by referring to information provided by pharmaceutical company representatives (16%).

Conclusion Most orthopedists prescribe some type of drug to prevent NSAID-induced ulcers but do not refer to the guidelines. We therefore strongly recommend that the guidelines be made more widely known to gastroenterologists and to physicians in every field of clinical practice, including orthopedics.

Key words: nonsteroidal anti-inflammatory drugs, proton pump inhibitor, H₂-receptor antagonist, gastroprotective drugs

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most frequently prescribed drugs, particularly in the field of orthopedics (1). Twenty million Americans regularly use NSAIDs, and more than 111 million prescriptions for NSAIDs are written each year (2). Despite their indisputable efficacy, NSAIDs can pose a dilemma for doctors due to their possible gastrointestinal complications (3). Use of NSAIDs is the second most common cause, after *Helicobacter pylori* infection, of gastroduodenal ulcers, and the relative risk of a serious gastrointestinal adverse event is approximately three times greater in users of NSAIDs than in nonusers (4, 5). The concomitant use of cytoprotective drugs lowers the risk of NSAID-induced gastrointestinal complications (6). Recently, guidelines for the treatment and prevention of NSAID-induced ulcers were established. The guidelines are consistent in identifying certain characteristics of high-risk NSAID users based on data from observational studies. Higher age, prior upper gastrointestinal events, and concurrent use of warfarin have been identified as risk in each of these guidelines on the basis of consistent findings from epidemiologic studies. Some observational studies have also identified concurrent corticosteroid use and high-dose corticosteroid use as risk factors. Thus, these additional risk factors are included in most guidelines (7-9). Each of the guidelines provides several options for preventing NSAID-related upper gastrointestinal events (2). Histamine H₂-receptor antagonists (H₂RAs), proton pump inhibitors (PPIs) and prostaglandin analogues (PAs) have been shown to reduce gastrointestinal injury related to NSAIDs. However, gastroprotective agents are prescribed with NSAIDs in only 17% to 34% of cases (10). On the other hand, understanding the roles of both isoforms of cyclo-oxygenase (COX) has led to new drugs being developed in recent years, and selective COX-2 inhibitors have been marketed to minimize gastrointestinal toxicity while maintaining anti-inflammatory activity (11). The guidelines recommend the use of selective COX-2 inhibitors in patients with risk factors for NSAID-associated gastrointestinal toxicity.

In Japan, COX-2 selective inhibitors are not available, and co-prescriptions of PPIs and regular-dose H₂RAs for the prevention of NSAID-induced ulcers are not allowed by the Ministry of Health, Labour and Welfare. The aim of the present study was to examine factors in the use by orthopedists in Japan of cytoprotective drugs to prevent NSAID-associated gastrointestinal adverse events.

Methods

We sent a questionnaire to 402 orthopedists in Hyogo Prefecture, Japan. A standardized 10-item questionnaire was used to collect information on NSAID prescriptions (drug name, pharmaceutical form, doses, duration of use) and associated drugs (especially gastroprotective agents). The con-

Table 1. The Distribution of NSAIDs Indication Disease

disease	n
discogenic hernia	204
rheumatoid arthritis	203
osteoarthritis	202
humeral articulationitis	202
sciatic neuralgia	202
spondylosis	199
lumbago	198
compression fracture	195
osteoporosis	78
others	99

tents of the questionnaire are described below.

1. When did you graduate from medical school, and what is your affiliation?
2. For what diseases are NSAIDs prescribed? (multiple answers were accepted)
3. List the first and the second most-frequent NSAID you prescribe
4. How long do you prescribe NSAIDs? (On demand, less than 3 months, more than 3 months)
5. Have you had patients who complained of abdominal symptoms during NSAID treatment in the last year?
6. What kind and what dosage of drugs do you prescribe for patients with abdominal symptoms during NSAID treatment? (PPIs, H₂RAs, PAs, gastroprotective drugs)
7. Are you satisfied with the symptom-reducing effects of gastroprotective agents?
8. Did any patients have hematemesis or melena during NSAID treatment?
9. What kind and dosage of drugs do you prescribe to prevent NSAID-associated gastrointestinal events? (PPIs, H₂-RAs, PAs, gastroprotective drugs)
10. Please write down the reasons you prescribe medicines for NSAID-associated gastrointestinal events and the information source to which you refer (including purpose of treatment and preventive administration).

Results

Two hundred eight (51.7%) orthopedists returned the questionnaire. Sixty-seven were working in their own office, 106 were working at a hospital, and 35 were at a university hospital. The return rate of the questionnaire was 56.8% from doctors working in their own office, 44.0% from doctors working at a hospital, and 81.4% from doctors working at a university hospital. The distribution of indicating diseases is shown in Table 1. The most frequently used NSAIDs were, in descending order, loxoprofen sodium, diclofenac sodium, and etodolac (Fig. 1). The distribution of

Figure 1. Ratio of prescription of common NSAIDs. Loxoprofen sodium was the most used drugs.

Table 2. The Distribution of NSAIDs Prescription Duration

duration	%
Less than 3 months	73
More than 3 months	15
On demand	12

Table 3. Drugs Prescribed to Prevent NSAIDs Associated Gastrointestinal Disease

Drugs	Distribution n(%)	Single use ratio %
gastroprotective drugs	185(44.6)	69.1
PA	72(17.4)	84.2
H2RA	81(19.5)	65.1
PPI	45(10.8)	67.7
others	32(7.7)	37

PA:prostaglandin analogues H2RA:Histamine H2 receptor antagonists

PPI:proton pump inhibitors

prescription durations is shown in Table 2. Seventy-five percent of doctors prescribed NSAIDs less than 3 months. Most doctors (80%) had patients with abdominal symptoms associated with NSAID use. Of these orthopedists, 59% treated such patients by themselves and prescribed gastroprotective drugs (32.2%), H2RAs (26.4%), PAs (17.0%), or PPIs (16.2%). The first choice of medication for the symptoms was gastroprotective drugs, such as rebamipide (56.0%) and teprenone (33.0%). Sixty-seven percent of doctors reported that these drugs reduced symptoms. Twenty-eight percent of doctors reported patients who had hematemesis or melena during NSAID treatment. Most orthopedists (96%) prescribed some type of drug to prevent NSAID-associated gastrointestinal events; the agents prescribed were gastroprotective drugs (44.6%), H2RAs (19.5%), PAs (17.4%), and PPIs (10.8%) (Table 3). The first-line drugs chosen were gastroprotective drugs in 98% of cases, PAs in 1%, and H2RAs in 1% (Table 4). The doctors reported that they prescribed medicine for NSAID-associated gastrointestinal events on the basis of their experience (23%), by considering medical insurance restrictions (17%), and by referring to information provided by pharmaceutical company representatives (16%). Only 4% of doctors observed guideline recommendations (Table 5). There were no significant differences in the present data among doctors

Table 4. Prescription to Prevent NSAIDs Associated Gastrointestinal Disease

Drugs (first choice)	%
gastroprotective drugs	98
PA	1
H2R	1

working in their own office, at a hospital, and at a university hospital.

Discussion

NSAIDs are known to cause gastrointestinal injury. Patients taking NSAIDs for rheumatoid arthritis or osteoarthritis have an ulcer incidence of 15% to 20% (12, 13). Complications of ulcer disease, i.e., hemorrhage and perforation, occur far more often in patients who are taking these agents than in patients who are not (14-16). Patients who are elderly, concurrently use corticosteroids or anticoagulants, have a history of peptic ulcer, or use a high average daily dose of NSAIDs are at increased risk of gastrointestinal events (2).

The guidelines in the United States for the prevention of NSAID-induced ulcers recommend misoprostol

Table 5. The Reason of Prescription to Prevent NSAID-associated Gastrointestinal Disease or the Information Source to Refer

reason /information	%
experience	23
medical insurance restriction	17
information of pharmacy persons	16
easiness to use	14
demand from patients	10
information of learned society	7
guideline of gastric ulcer	4
others	9
Total	100

(prostaglandins) or PPIs as prophylactic agents. In contrast, H2RAs have been shown to prevent only duodenal ulcer and, therefore, have not been recommended for prophylaxis (7). Although the use of selective COX-2 inhibitors is another option to reduce gastrointestinal mucosal injury, they have recently been shown to increase the incidence of cardiovascular adverse events (17-19), and the widespread use of selective COX-2 inhibitors has been discouraged.

Guidelines for gastric ulcers were also published in 2003

in Japan (20) and state that PAs, PPIs, and high-dose H2-RAs are effective for the preventions of NSAID-induced ulcer. In this study, we found that most orthopedists prescribe some type of drug to prevent NSAID-associated gastrointestinal events but do not refer to the guidelines. Only 4% of doctors observed the guidelines' recommendations. Other doctors prescribed the medicine on the basis of their experience, by considering medical insurance restrictions, or by referring to information provided by pharmaceutical company representatives. The present data were obtained from questionnaires and the return rate of questionnaires was relatively low, especially from doctors working in their own office or at a hospital. Therefore, there were some limitations and bias in the data. However, there were no significant differences in the present data according to the affiliation of doctors. Even for doctors working at a university hospital, only 6.7% observed the guidelines' recommendations. Therefore, our data describe the present situation regarding the prescription of NSAIDs and co-prescribed drugs for mucosal protection among orthopedists in Japan.

We, therefore, strongly recommend that the guidelines should be made more widely known to gastroenterologists and to physicians in every field of clinical practice, including orthopedics. Furthermore, as very little evidence is available concerning the prophylaxis of NSAID-induced mucosal injury in Japan, randomized control trials of the effectiveness of PPIs, H2RAs, and gastroprotective drugs, which are mainly used in Japan to prevent NSAID-induced ulcers, should be performed.

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