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The Pattern of Use of Oral NSAIDs with or without Co-prescription of Gastroprotective Agent for Arthritic Knee by Korean Practitioners

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Purpose: The aim of this study was to describe the patterns of use of non-steroidal anti-inflammatory drugs (NSAIDs) for arthritic knees in clinical practice, particularly focusing on the co-prescription of gastroprotective agents for patients with risk factors for adverse gastrointestinal (GI) events.
Materials and Methods: Each cross-sectional cohort was a group of outpatients visiting 111 physicians who had prescribed NSAIDs for the patients' arthritic knees for more than three consecutive months. A self-administered questionnaire was completed by each patient and physician.
Results: Nine hundred and forty five patients (48%) of the whole 1,960 patients belonged to the group with a high or very high risk for NSAID-induced gastropathy determined by northern California Health Maintenance Organization guidelines. Overall, only less than half of the patients were given co-prescription of gastroprotective agents, regardless of the presence or absence of GI symptoms and irrespective of the level of risk for NSAID-induced gastropathy.
Conclusions: The physician prescribing NSAIDs for arthritic knees should monitor any GI symptoms and the patient monitor anylevel for NSAID-induced gastropathy, and be willing to add gastroprotective agents as necessary in order to prevent serious adverse GI events.

Key words: **Knee, Arthritis, Non-steroidal anti-inflammatory drugs, Gastroprotective agents, Co-prescription.**

Introduction

Risk factors for development of gastrointestinal (GI) toxicity in patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) for arthritis or other musculoskeletal diseases include[1-5] prior history of complicated or uncomplicated ulcers; increased age; multiple NSAID use; high NSAID dose; concomitant use of corticosteroids or anticoagulants including acetylsalicylic acid[6]; concomitant *Helicobactor pylori* (*H. pylori*) infection[7,8]; comorbidities, such as significant cardiovascular disease; female gender9; and severe rheumatoid arthritis.

Most global and domestic guidelines for clinical practitioners recommend the use of either a cyclooxygenase-2 (COX-2) selective agent or a nonselective NSAID with co-prescription of gastroprotective agents in patients with the risk factors[3-5].

The aim of this study was to describe the patterns of use of NSAIDs for arthritic knees in clinical practice in Korea, particularly focusing on the co-prescription of gastroprotective agents for patients with or without the risk factors for GI toxicity or adverse GI events.

Materials and Methods

A survey was performed in the ambulatory of 82 hospitals (62 university and 20 general hospitals) where 111 physicians, members of the Korean Knee Society, had prescribed NSAIDs to

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relieve symptoms and signs of arthritic knees for more than three consecutive months. This cross-sectional observational study was performed on a single day between August and October 2009, although the exact date of study was different among the survey sites.

All the patients were ≥20 years old, had been taking oral NSAIDs for more than three consecutive months, and required additional prescription of NSAIDs for symptomatic relief of their arthritic knees. A self-administered questionnaire was completed by each of the 2,000 patients who fulfilled those inclusion criteria and by the physicians to get the information of the recent and current prescriptions. The questionnaire for the patient included questions on the risk factors for GI adverse effects, such as age, gender, general condition, any history of peptic ulcer with or without hemorrhage or perforation, concomitant use of anticoagulants or corticosteroids, concomitant *H. pylori* infection, and comorbidities, such as significant cardiovascular disease. It also included questions about the status of the affected knee joint and any adverse GI symptoms. The data from the questionnaires filled up by the physicians were analyzed to investigate the prescribing habits of NSAIDs and gastroprotective agents and to determine whether the physicians took any GI symptoms and the patient's own risk level into consideration when they prescribed medicine.

The patients were stratified according to the risk of developing adverse GI events by using the Standardized Calculator of Risk for Events (SCORE) tool. The SCORE had been developed at Stanford University[1] and become the base of the treatment guidelines for the use of NSAIDs that was disseminated by northern California Health Maintenance Organization (HMO). The SCORE tool assigned points for six patient factors including age, gender, morbidity, GI problems, and rheumatoid. Whereas the HMO classification categorized patients as level 1 or lowest risk (1-15 points), level 2 or intermediate risk (16-20 points), and level 3 risk (21 points or greater)[9] we classified the patients into low risk (1-10 points), moderate risk (11-15 points), high risk (16-20 points), and very high risk (21 points or greater) of developing serious GI complications.

Table 1. The Prevalence of Risk Factors for Gastrointestinal (GI) Toxicity (n=1,960)

Risk factors	No. of cases (%)
Age ≥ 65 years	1,095 (56)
Prior history GI adverse events	784 (40)
Comorbidities	490 (25)
Concomitant use of corticosteroids	275 (14)
Rheumatoid arthritis	197 (10)
Concomitant use of aspirin	117 (6)
Concomitant use of anticoagulant	39 (2)
Prior history of admission for serious GI adverse events	39 (2)
Poor general condition	20 (1)

Percentage total more than 100% because of concurrent risk factors.

Results

Of the 2,000 patients who completed the questionnaire, 1,960 met the eligibility criteria based on the rules for inclusion and exclusion. Fifty-six per cent of the subjects were more than 65 years of age and 76% were female.

Table 1 presents the prevalence of individual risk factor for GI complications. One hundred and sixty patients (8%) were at very high GI risk, and 785 patients (40%) were considered at high risk for adverse GI events (Table 2).

Among the patients in a high or very high risk group, 321 patients (34%) had a prescription of COX-2 inhibitors, 331 patients (35%) nonselective NSAIDs without co-prescription of gastroprotective agents, and 293 patients (31%) nonselective NSAIDs plus gastroprotective agents (Table 3). This means, among 542 high or very high-risk patients taking NSAIDs without the co-prescription of gastroprotective agents, 331 patients (61%) were given non-selective NSAIDs instead

Table 2. Patients Stratified by Risk of Developing Gastrointestinal Complications using SCORE Tool (n=1,960)

Risk level (level determined by HMO guideline[9])	No. of cases (%)
Very high > 21 points (level 3)	160 (8)
High 16-20 points (level 2)	785 (40)
Moderate 11-15 points (level 1)	784 (40)
Low < 11 points (level 1)	231 (12)

SCORE: standardized calculator of risk for events, HMO: health maintenance organization.

Table 3. NSAID Prescribed in Patients with High or Very High Risk for GI Toxicity (n=945)

NSAIDs prescribed	No. of cases (%)
Coxibs without gastroprotective agents	211 (22)
Coxibs with gastroprotective agents	110 (12)
Non-selective NSAIDs without gastroprotective agents	331 (35)
Non-selective NSAIDs with gastroprotective agents	293 (31)

NSAID: non-steroidal anti-inflammatory drug, GI: gastrointestinal, Coxibs: cyclooxygenase-2 selective NSAIDs.

Table 4. Utilization of Coxibs in Patients with or without GI Risks or Symptoms

Patients taking NSAIDs	Coxibs
High or very high risk group (n=945)	321 (34)
Moderate or low risk group (n=1,015)	162 (16)
With GI symptoms (n=941)	223 (24)
No GI symptoms (n=1,019)	260 (26)

Values are presented as number (%).
NSAID: non-steroidal anti-inflammatory drug, GI: gastrointestinal, Coxibs: cyclooxygenase-2 selective NSAIDs.

Table 5. Prevalence of Use of Gastroprotective Agents in Patients Taking Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Patients taking NSAIDs	Gastroprotection
High or very high risk group (n=945)	406 (43)
Moderate or low risk group (n=1,015)	399 (39)
With GI symptoms (n=941)	412 (44)
No GI symptoms (n=1,019)	393 (39)

Values are presented as number (%).

Table 6. Types of Gastroprotective Therapy (n=805)

Gastroprotective agents	No. of patients (%)
Cytoprotectant	347 (43)
Rebamipide	255 (32)
Ecabet sodium granules	24 (3)
H_2RA	191 (24)
Rranitidine	105 (13)
Cimetidine	23 (3)
Gastroprokinetics	107 (13)
Levosulpride	27 (3)
Mosapride	25 (3)
Itopride	24 (3)
Domperidone	23 (3)
PPI	71 (9)
Pantoprazole	42 (5)
Others	268 (33)

Percentage total more than 100% because of concomitant use.
H_2RA: histamine$_2$-receptor antagonist, PPI: proton pump inhibitor.

of selective NSAIDs. Whether the patients had adverse GI symptoms or not did not affect the proportion of patients taking selective NSAIDs (Table 4).

Overall, a gastroprotective therapy was performed in 805 (41%) patients and only less than half of the patients were given co-prescription of gastroprotective agents regardless of the presence or absence of GI symptoms and irrespective of the level of risk for NSAID-induced gastropathy (Table 5). Among the patients using the preventive drugs, 255 (32%) patients received rebamipide whereas histamine$_2$ (H_2)-receptor antagonists (H_2RA) were coprescribed for 191 (24%) patients (Table 6).

Discussion

The most frequent and significant adverse effect associated with NSAIDs is GI toxicity. The symptoms of GI toxicity include both annoying maladies, such as dyspepsia or disgust, and serious events, such as GI ulcers with hemorrhage or perforation.

Despite all global and domestic guidelines recommending the use of either a COX-2 inhibitor or a nonselective NSAID with co-prescription of gastroprotective agents for patients who are at risk of developing GI toxicity, almost thirty-five per cent of the patients at high or very high risk took nonselective NSAIDs without co-prescription of gastroprotective agents in this study. Besides, more than half of the patients complaining of GI symptoms were not given co-prescription of gastroprotective agents, and only a quarter of the patients complaining of GI symptoms were given prescription of selective COX-2 inhibitors in this study.

Overall, only less than half of the patients were given co-prescription of gastroprotective agents regardless of the presence or absence of GI symptoms and irrespective of the level of risk for NSAID-induced gastropathy. There have been disparities between medication guidelines and government's reimbursement policies which may modify the enthusiasm of some practitioners for gastroprotection.

With regard to gastroprotective agents, proton pump inhibitor (PPI) or misoprostol has been widely recognized as the most effective one[10]. PPIs including omeprazole, lansoprazole[11], and esomeprazole[12] significantly reduced symptomatic ulcers among patients receiving NSAIDs. However, one must also consider potential complications of the long-term PPI use including acceleration of corpus atrophy and, possibly, its role in hip fractures, pneumonia, and pseudomembranous colitis[8]. It has been shown that the incidence of peptic ulcers associated with NSAID use can be reduced by cotherapy with the synthetic prostaglandin misoprostol. However, poor tolerability is a major limitation of the drug. In a clinical trial[13], 27.5% of misoprostol-treated patients withdrew prematurely from the study due to adverse events, most of which were GI complaints including abdominal pain and diarrhea.

Although most global and domestic guidelines recommend the use of PPI or misoprostol for gastroprotection[3-5], other

options that might reduce the risk for NSAID-related upper GI complications are also available. Symptomatic low risk patients without evidence of blood loss may switch to another NSAID (or coxib) or receive treatment with antacids or H_2RA[10].

Selective COX-2 inhibitors (coxibs) are safer to the GI tract than traditional NSAIDs. However, current prevention strategies for patients who need NSAIDs should also take into account the presence of cardiovascular (CV) risk factors, as coxibs and probably post traditional NSAIDs increase the incidence of serious CV events[2]. Moreover, the introduction of coxibs has not completely eliminated GI adverse events. There have been several reports that COX-2-inhibitor users did not have a reduced risk of a GI bleed compared with patients using nonselective NSAIDs[14]. Currently, it is accepted that the choice of an NSAID should be determined by the need to balance each patient's GI and CV risks. Several trials with less potent COX-1 inhibitors showed significant reductions in endoscopic gastric ulcers and erosions[10,15,16]. The development of COX-2-selective inhibitors and the formation of other new, safer inhibitors should broaden the range of options.

Although acid inhibitors may relieve symptoms, they have not been proven to reduce GI complications, Among H_2RA, only high dose of famotidine has been recognized as a gastroprotective agent in most official guidelines. Recent improvements in the understanding of NSAID-induced damage and new gastroprotective agent development[17] would provide an opportunity for effective anti-inflammatory with reduced GI complications.

In summary, strategies for reducing the risk for NSAID-related GI complications remain underused even in high-risk patients and patients with GI symptoms. Thus, the physician prescribing NSAIDS for arthritic knees should determine the level of patient's own risk for NSAID-induced gastropathy, monitor any developing GI symptoms, and be willing to prescribe gastroprotective agents for the patient, in order to prevent serious adverse events. Also, the ultimate choice of therapy for a particular patient depends on several things including risk factors, the preferences of the patient and the physician, and cost[10].

Conclusions

The physician prescribing NSAIDS for arthritic knees should monitor any developing GI symptoms or the level of patient's own risk for gastropathy, and be willing to add gastroprotective agents for the patient in order to prevent serious adverse events.

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