Mod Rheumatol (2003) 13:143–152

ORIGINAL ARTICLE

Tetsuya Tomita · Takahiro Ochi · Kentaro Sugano
Shinichi Uemura · Robert W. Makuch

Systematic review of NSAID-induced adverse reactions in patients with rheumatoid arthritis in Japan

Received: April 24, 2002 / Accepted: September 11, 2002

Abstract A systematic review of randomized controlled clinical trials of nonsteroidal antiinflammatory drugs (NSAIDs) in rheumatoid arthritis (RA) patients was conducted to evaluate the risk of NSAID-induced adverse reactions. Double-blind, randomized, controlled trials with 6-week treatments for RA patients were included in the study. The endpoints for the analysis included any adverse reactions, digestive adverse reactions, and upper gastrointestinal (GI) adverse reactions. A fixed-effect model was used for estimation of the risk. Time-to-event analysis of the incidence of adverse reactions was also conducted. A total of 28 trials was included for the analysis, and a total of 30 NSAIDs were used in the trials. The proportion of patients who experienced any adverse reaction was as follows: piroxicam 18.9% (3 trials), diclofenac 18.8% (4 trials), indomethacin 22.1% (14 trials), and aspirin 25.0% (4 trials). The proportion of patients who experienced digestive adverse reactions was as follows: piroxicam 10.2%, diclofenac 10.6%, indomethacin 13.1%, and aspirin 14.1%. Most withdrawals due to adverse reaction occurred during the first 3 weeks after administration of the NSAID. Although the risk of NSAID-induced adverse reaction was different from drug to drug, the risk of adverse reaction was clinically significant.

Key words Nonsteroidal antiinflammatory drugs (NSAIDs) · Rheumatoid arthritis (RA) · Systematic review · Tolerability

T. Tomita · T. Ochi
Department of Orthopedics, Osaka University Graduate School of Medicine, Osaka Japan

K. Sugano
Department of Gastroenterology, Jichi Medical School, Tochigi, Japan

S. Uemura[1] (✉)
Biostatistics, Department of Health Science & Nursing, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

R.W. Makuch
Division of Biostatistics, Department of Epidemiology and Public Health, School of Medicine, Yale University, New Haven, CT, USA

Present address:
[1] Department of Epidemiology and Environmental Health, Graduate School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japn
Tel. +81-3-5802-1047; Fax +81-3-3812-1026
e-mail: uemura@zap.att.ne.jp

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease of the joints that causes serious morbidity and disability for the patients. For successful treatment to minimize joint damage, functional loss, and pain, early diagnosis and timely initiation of pharmacological agents are required. According to the Guideline for the Management of Rheumatoid Arthritis in the United States,[1] essential components of the management of RA suggest initial treatment with nonsteroidal antiinflammatory drugs (NSAIDs), use of disease-modifying antirheumatic drugs (DMARDs), and possible use of local or low-dose oral glucocorticoids. Because DMARDs have the potential to reduce or prevent joint damage and preserve joint integrity and function, they have recently received more attention in RA treatment. However, the role of NSAIDs as the initial palliative drug therapy to reduce joint inflammation and pain is still clinically important.[2,3]

Because of the nature of long-term treatment of RA, sufficient attention must be paid not only to the efficacy of drugs but also to their safety. Common adverse reactions to NSAIDs, including gastrointestinal (GI) disorder, renal disorder, hepatic disorder, asthma, allergic rash, and disturbed hematopoiesis are attributed to the inhibition of prostaglandin (PG) production. Among them, GI disorder is of particular safety concern.[4,5] Serious adverse reactions such as gastroduodenal ulcer, perforating ulcer, and GI hemorrhage resulting from damaged GI mucosa are clinically significant. In addition to these GI toxicities, GI symptoms including abdominal pain and dyspepsia should be closely observed because these subjective symptoms may disturb

prescription compliance during long-term treatment with these drugs. Silverstein et al.[6] reported that approximately 20% of RA patients (not taking GI remedies) assigned to take NSAIDs for 6 months in a clinical study had intolerable GI symptoms and, because of these events, dropped out from the study. The recently published results of a meta-analysis intended to compare the incidence of upper GI symptoms[7] and a large-scale study for safety evaluation of NSAIDs[8] revealed that the most common GI adverse reactions in patients receiving NSAIDs were dyspepsia, abdominal pain, and nausea/vomiting. Although some investigators claim that these GI symptoms do not necessarily predict more serious adverse drug reactions such as ulcer and bleeding, a relatively large number of patients complain of these symptoms, which may lead to dosage reduction, discontinuation of treatment, and modifications in the prescribed drugs.[9,10]

The safety profile of NSAIDs has been evaluated by various epidemiological investigations,[10,11] a large-scale clinical study,[8] and meta-analyses[12,13] in Europe and the United States. In Japan, the safety profile of NSAIDs has not been examined in detail, partly because the drugs of this class are used at lower doses compared to Europe and the United States. An epidemiological investigation sponsored by the Japan Rheumatism Foundation in 1991[14] is the only large-scale study in Japan, and these results might not reflect improvements in clinical practice. Several related research activities have recently been carried out in Japan, including a large-scale investigation of adverse drug reactions reported by the Rheumatism Friendship Association[15] and the establishment of a Japanese version of ARAMIS (J-ARAMIS[16]), a large-scale database system on antirheumatic therapy in the United States. However, the tolerability of NSAIDs has so far been evaluated by few researchers in Japan. This study was aimed, therefore, to systemically analyze the results of clinical studies of NSAIDs and thereby to evaluate the risk of adverse reactions to NSAIDs in Japan.

Materials and methods

Materials

Studies were included in this analysis if they were designed as double-blind, parallel-group, controlled studies intended to evaluate the efficacy and safety of NSAIDs in Japanese patients with RA; if they were performed in accordance with the Guidelines for Clinical Evaluation of Analgesic and Anti-inflammatory Drugs (revised)[17] and approved by the Ministry of Health, Labour and Welfare; if they were performed with drugs clinically available at present; and if the duration of treatment was at least 6 weeks. To cover all published papers, medical databases, i.e., MEDLINE, J-MEDICINE, and Japana Centra Revuo Medicina, in addition to literature listed in references of package inserts, were used. Additionally, a manual review of all original contribution papers from the following major Japanese journals was performed by two reviewers: *Ryumachi* (the official journal of the Japan Rheumatism Association), *Rinsho Hyoka* (*Clinical Evaluation*), *Ensyo* (*Japanese Journal of Inflammation*), *Igaku No Ayumi* (*Journal of Clinical and Experimental Medicine*), and *Rinsyo Iyaku* (*Journal of Clinical Therapeutics and Medicine*). One report for a study in which a drug was given for 12 weeks[18] was excluded from the analysis because it was impossible to identify adverse drug reactions observed during the first 6 weeks.

It has been recommended by the guideline to include at least 60 cases in each group. Because the recommended number of cases has not been statistically justified, no limitation was imposed on the number of cases in each study to be included in the analysis. Studies in which GI remedies were used in combination with NSAIDs were not included unless these remedies were simply treatments for GI symptoms. As a result of the literature screening, 28 reports were selected.[19–46] In the selected 28 studies, 30 different NSAIDs were described, 6 of which had been used in more than 1 study. Data on these six drugs were analyzed on a drug-to-drug basis. The remaining 24 drugs were classified according to chemical structure (modified from Sano et al.[47]) before analysis of data.

Methods

Endpoints

The primary endpoints of the analysis were occurrence of any adverse drug reactions, discontinuation of treatment because of adverse drug reactions, occurrence of GI adverse drug reactions, and occurrence of upper GI adverse drug reactions. In the meta-analysis of the tolerability for upper GI symptoms performed by Bensen et al.,[7] cumulative incidences were determined for moderate to severe abdominal pain, dyspepsia, and nausea/vomiting (composite endpoint). In our study, upper GI symptoms were analyzed on the basis of the composite endpoint and not individually for each symptom, because the number of cases analyzed was not sufficient to analyze the data on each type of symptom. Toxic symptoms were defined in accordance with the Adverse Drug Reaction Terminology.[48]

Statistical analysis

In this study, relatively few papers were found in which the two treatment groups being compared were identical; therefore, it was not possible to conduct a combined analysis of the odds ratios for the onset of events (data obtained from 2×2 contingency table) that would usually be performed with meta-analysis. Instead, the incidence of adverse drug reactions in each treatment arm was calculated, and the incidence data thus obtained from each drug or each drug group, classified according to basic chemical structure, were combined. Each study was regarded as a stratum; the incidences of adverse drug reactions in each strata were combined and the 95% confidence interval was estimated. Assuming that the incidence of adverse drug reactions in each study is the same in all strata, a fixed-effects model was

used to combine the results. The strata were combined by the generalized variance-based method in which the reciprocal of the variance of the binominal distribution was regarded as the weight of each study. The difference in the incidence of adverse drug reactions among studies (heterogeneity) was analyzed by chi-square test using degree of freedom (df) = (number of studies − 1).

Data from papers in which lists of cases of adverse drug reactions were available were used to construct a Kaplan–Meier curve consisting of time (the number of days of administration before the occurrence of adverse drug reaction) and event (the occurrence of adverse drug reaction), and from this the pattern of occurrence of adverse drug reactions was analyzed. Occurrence of any adverse drug reactions, discontinuation of treatment because of adverse drug reactions, and occurrence of upper GI adverse drug reactions were taken as endpoints, and a curve for each endpoint was constructed. When the curve for upper GI adverse drug reactions was constructed for cases withdrawn from the study because of symptoms other than those corresponding to the composite endpoint, the date of withdrawal was taken as censored.

To evaluate the effects of covariates on the occurrence of adverse drug reactions, the odds ratios for the occurrence of adverse drug reactions controlling for gender or age were calculated and compared. Because in some papers subjects had been classified according to 10-year age intervals, the subjects in this meta-analysis were divided into persons younger than 60 years old and those aged 60 years or older, and the odds ratio for the occurrence of adverse drug reactions in each subgroup of subjects was calculated. Assuming that the results of each study are the same in all strata, a fixed-effects model was used. Odds ratios in each study were combined by the Mantel–Haenszel method, and 95% confidence intervals for the combined odds ratio were calculated.

Results

Twenty-eight papers were selected and classified according to the chemical structure of the study drugs (Table 1). Drugs examined were indomethacin (15 studies), aspirin (5 studies), diclofenac (4 studies), piroxicam (3 studies), ketoprofen (2 studies), and tolfenamic acid (2 studies). Aspirin, indomethacin, and diclofenac sodium were frequently included in these studies as control drugs as recommended by the "Guidelines for Clinical Evaluation of Analgesic and Anti-inflammatory Drugs (revised)." Drugs were grouped into the following classes, based on the basic chemical structure: propionic acid (9 drugs), allyl acetate (9 drugs), oxicam (4 drugs), and carbonic acid (2 studies).

Demographic characteristics

Demographic characteristics classified according to drug and chemical structure are shown in Table 2. The number of cases recorded in the selected 28 papers was 4616, consisting of 739 males (16.0%) and 3877 females (84.0%). Subjects in their fifties were most common (32.5%), followed by subjects aged 60 years or older (24.6%) and those in their forties (21.9%). Demographic data on sex and age from each paper were summarized.

Incidence of any adverse drug reactions

The incidence of any adverse drug reactions was analyzed (Table 3). Adverse drug reactions were most common with aspirin, with the combined incidence in five studies being 29.2% (95% CI, 25.1%–33.3%). The heterogeneity in these five studies was chi-square (df) = 62.34 (4), $P < 0.001$. Second, the combined incidence of adverse drug reactions with indomethacin in 15 studies was 21.7% (95% CI, 19.5%–23.9%). The heterogeneity in these 15 studies was chi-square (df) = 27.32 (14), $P = 0.017$. The incidence of adverse drug reactions among all the other drugs was as follows: ketoprofen (20.4%; 95% CI, 14.1%–26.7%), piroxicam (18.9%; 95% CI, 14.2%–23.7%), tolfenamic acid (18.9%; 95% CI, 11.7%–26.0%), and diclofenac (18.8%; 95% CI, 14.3%–23.4%). The incidence of adverse drug reactions determined in each group of drugs classified according to basic chemical structure was lowest with oxicam drugs, a group that included four different drugs. There was no difference in the incidence of adverse drug reactions among the studies in the oxicam group (heterogeneity test: chi-square [(df) = 5.71 (3), $P = 0.127$], with the combined incidence of adverse drug reactions being 12.7% (95% CI, 9.5%–15.9%). The next highest incidence of adverse drug reactions was with the propionic acids group at 15.1% (95% CI, 12.6%–17.6%) [heterogeneity test: chi-square (df) = 7.23 (8), $P = 0.512$]. The combined incidence of adverse drug reactions with allyl acetates was 15.2% (95 CI, 12.8%–17.6%), with this incidence being highly variable across the included studies [heterogeneity test: chi-square (df) = 26.97 (7), $P = 0.001$].

Incidence of adverse GI drug reactions

The incidence of adverse GI drug reactions was analyzed (Table 4). Papers not recording the number of cases of adverse GI drug reactions were excluded from the analysis. Adverse GI drug reactions were most common with aspirin, a finding consistent with the occurrence of any adverse drug reactions, with a combined incidence of 14.1% (95% CI, 10.1%–18.2%). The heterogeneity of these studies was chi-square (df) = 12.13 (2), $P = 0.007$. Second, the combined incidence of adverse drug reactions with indomethacin was 13.0% (95% CI, 11.2%–14.9%). The heterogeneity of in these studies was chi-square (df) = 22.58 (14), $P = 0.067$. The incidence of adverse GI drug reactions among all other drugs was as follows: diclofenac (10.6%; 95% CI, 6.2%–15.0%), piroxicam (10.2%; 95% CI, 6.0%–14.3%), and tolfenamic acid (7.2%; 95% CI, 2.6%–11.8%).

The incidence of adverse drug reactions determined in each group of drugs classified according to basic chemical

Table 1. Double-blind randomized controlled trials of NSAIDs for RA

Basic chemical characteristics	References number	Test drug: Comparison	Dose (mg)	Year	*N*
Carboxylic acid					
Salicylic acid	19	Diflunisal:	750	1983	90
		Aspirin	2600		95
Anthtanilic acid	20	Floctafenine:	600	1985	88
		Aspirin	2500		90
	21	Tolfenamic acid:	300	1981	80
		Indomethacin	75		78
	22	Tolfenamic acid:	300	1986	39
		Diclofenac	75		34
Allyle acetate					
Phenyl acetate	23	Alclofenac:	2250	1980	72
		Indomethacin	75		82
	24	Amfenac:	200	1982	73
		Indomethacin	75		64
	25	Diclofenac SR:	75	1988	99
		Diclofenac	75		98
Indole acetate	26	Sulindac:	300	1979	77
		Indomethacin	75		79
	27	Acemetacin:	90	1981	86
		Indomethacin	75		82
	28	Proglumetacin maleate:	270	1986	84
		Diclofenac	100		96
	29	Indomethacin farnesil:	400	1989	91
		Indomethacin	75		101
Naphthalene acetate	30	Nabumeton:	800	1987	98
		Indomethacin	75		98
Pyrano acetate	31	Etodolac:	400	1991	107
		Indomethacin	75		113
Propionic acid					
Phenyl	32	Ketoprofen:	50	1978	56
		Aspirin	3000		54
	33	Fenoprofen calcium:	1800	1981	100
		Aspirin	2400		91
	34	Loxoprofen:	180	1985	110
		Indomethacin	75		116
	35	Alminoprofen:	600	1986	92
		Indomethacin	75		95
	36	Ketoprofen SR:	150	1989	106
		Ketoprofen	50		94
Thiophene	37	Tiaprofen acid:	600	1982	70
		Indomethacin	75		68
Naphtalene	38	Naproxen:	600	1978	83
		Phenylbutazone	300		81
Tricyclic	39	Pranoprofen:	300	1979	72
		Aspirin	2400		74
	40	Zaltoprofen:	240	1991	77
		Diclofenac	75		73
Diphenyl Oxazole	41	Oxaprozin:	400	1984	86
		Diclofenac	75		79
Oxicam	42	Piroxicam:	20	1980	53
		Indomethacin	75		55
	43	Tenoxicam:	20	1984	100
		Indomethacin	75		96
	44	Ampiroxicam:	27	1991	106
		Piroxicam	20		108
	45	Lornoxicam:	12	1997	91
		Indomethacin	75		92
	46	Meloxicam:	10	1997	104
		Piroxicam	20		97

NSAID, nonsteroidal antiinflammatory drug; RA, rheumatoid arthritis

structure was again lowest with oxicam drugs. There was no difference in the incidence of adverse drug reactions among the oxicam studies [heterogeneity test: chi-square (*df*) = 3.99 (3), $P = 0.262$], with the combined incidence of adverse drug reactions being 6.1% (95% CI, 3.8%–8.5%). The combined incidence of adverse drug reactions with propionic acids was 9.3% (95% CI, 6.8%–11.8%) [heterogeneity test: chi-square (*df*) = 20.07 (6), $P < 0.001$]. The combined incidence of adverse drug reactions with allyl acetates was 7.55% (95 CI, 5.7%–9.4%), with the incidence varying

Table 2. Patient demographic characteristics

	By drug						By basic chemical characteristics				
	IND	ASP	DF	PIX	TRF	KTP	PRP[a]	ALY[b]	OXM[c]	CAL[d]	Sum
Number of study	15	5	4	3	2	2	9	9	4	2	55
N	1251	404	277	258	121	150	796	780	401	178	4616
Sex (%)											
Male	15.7	15.1	18.8	15.5	16.5	17.3	15.6	14.5	18.7	17.4	16.0
Female	84.3	84.9	81.2	84.5	83.5	82.7	84.4	85.5	81.3	82.6	84.0
Age											
10s	0.1	0.2	0.0	0.0	0.0	0.7	1.2	0	0.0	0.0	0.2
20s	2.2	4.2	2.5	2.7	2.5	2.0	10.2	9.4	2.5	4.5	3.2
30s	11.2	12.6	9.0	9.3	14.9	7.3	24.8	37.5	7.2	10.7	11.1
40s	22.1	21.8	19.1	19.4	24.8	20.7	50.1	66.6	19.0	21.3	21.9
50s	30.5	34.9	34.7	33.3	32.2	39.3	56.1	101.9	35.4	33.1	32.5
60s	25.6	19.6	28.9	32.6	19.8	23.3	45.3	70.6	28.2	22.5	24.6
70s+	8.3	6.7	5.8	2.7	5.8	6.7	12.3	14.1	7.7	7.9	6.5

IND, indomethacin (75 mg/day); ASP, aspirin (2400–3000 mg/day); DF, diclofenac (75 mg/day); PIX, piroxicam (20 mg/day); TRF, tolfenamic acid (300 mg/day); KTP, Ketoprofen (50 mg/day); PRP, propionic acid; ALY, allyle acetate; OXM, oxicam; CAL, carboxylic acide
[a] Loxoprofen, alminoprofen, ketoprofen SR, tiaprofen acid, zaltoprofen, oxaprozin, naproxen, pranoprofen
[b] Amfenac, alclofenac, fenoprofen Ca, diclofenac SR, acemetacin, sulindac, proglumetacin maleate, nabumeton, etodolac, indomethacin farnesil
[c] Ampiroxicam, tenoxicam, lornoxicam, meloxicam
[d] Diflunisal, floctafenine

Table 3. Cumulative incidence of any adverse reaction and its 95% confidence interval (CI)

Drug	Number of study	*N*	%	95% CI		Test of heterogeneity	*P*
				Lower	Upper		
Drug							
Tolfenamic acid (300 mg/day)	2	119	18.3	11.3	25.2	$\chi^2(df) = 0.40\ (1)$	$P = 0.528$
Diclofenac (75 mg/day)	4	284	18.8	14.3	23.4	$\chi^2(df) = 0.83\ (3)$	$P = 0.843$
Piroxicam (20 mg/day)	3	258	18.9	14.2	23.7	$\chi^2(df) = 4.09\ (2)$	$P = 0.129$
Ketoprofen (50 mg/day)	2	150	20.4	14.1	26.7	$\chi^2(df) = 9.24\ (1)$	$P = 0.002$
Indomethacin (75 mg/day)	15	1315	21.7	19.5	23.9	$\chi^2(df) = 27.32\ (14)$	$P = 0.017$
Aspirin (2400–3000 mg/day)	5	404	29.2	25.1	33.3	$\chi^2(df) = 62.34\ (4)$	$P < 0.001$
Basic chemical characteristics							
Oxicam[a]	4	401	12.7	9.4	15.9	$\chi^2(df) = 5.71\ (3)$	$P = 0.127$
Propionic acid[b]	9	796	15.1	12.6	17.6	$\chi^2(df) = 7.23\ (8)$	$P = 0.512$
Allyle acetate[c]	9	787	15.2	12.8	17.7	$\chi^2(df) = 30.43\ (8)$	$P < 0.001$
Carboxylic[d]	2	178	16.2	10.8	21.6	$\chi^2(df) = 0.30\ (1)$	$P = 0.587$
Total	55	4692	18.1	17.0	19.2		

[a] Ampiroxicam, lornoxicam, meloxicam, tenoxicam
[b] Alminoprofen, fenoprofen Ca, ketoprofen SR, loxoprofen, naproxen, oxaprozin, pranoprofen, tiaprofen acid, zaltoprofen
[c] Acemetacin, alclofenac, amfenac, diclofenac SR, etodolac, fenoprofen Ca, indometacin farnesil, nabumeton, proglumetacin maleate, sulindac
[d] Diflunisal, floctafenine

Table 4. Cumulative incidence of any adverse digestive reaction and its 95% confidence interval (CI)

Drug	Number of study	*N*	%	95%CI		Test of heterogeneity	*P*
				Lower	Upper		
Drug							
Tolfenamic acid (300 mg/day)	2	119	7.2	2.6	11.8	$\chi^2(df) = 0.52\ (1)$	$P = 0.471$
Piroxicam (20 mg/day)	2	205	10.2	6.0	14.3	$\chi^2(df) = 0.19\ (1)$	$P = 0.664$
Diclofenac (75 mg/day)	3	186	10.6	6.2	15.0	$\chi^2(df) = 1.76\ (2)$	$P = 0.415$
Indomethacin (75 mg/day)	15	1315	13.0	11.2	14.9	$\chi^2(df) = 22.58\ (14)$	$P = 0.067$
Aspirin (2400–2600 mg/day)	3	259	14.1	10.1	18.2	$\chi^2(df) = 22.51\ (2)$	$P < 0.001$
Basic chemical characteristics							
Oxicam[a]	4	401	6.1	3.8	8.5	$\chi^2(df) = 3.99\ (3)$	$P = 0.262$
Allyle acetate[b]	9	787	7.6	5.7	9.4	$\chi^2(df) = 28.36\ (8)$	$P < 0.001$
Carboxylic[c]	2	178	8.2	4.1	12.2	$\chi^2(df) = 0.59\ (1)$	$P = 0.443$
Propionic acid[d]	7	590	9.3	6.8	11.8	$\chi^2(df) = 15.58\ (6)$	$P = 0.016$
Total	47	4040	8.7	7.9	9.6		

[a] Ampiroxicam, lornoxicam, meloxicam, tenoxicam
[b] Acemetacin, alclofenac, amfenac, diclofenac SR, etodolac, fenoprofen Ca, indomethacin farnesil, nabumeton, proglumetacin maleate, sulindac
[c] Alminoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, tiaprofen acid, zaltoprofen
[d] Diflunisal, floctafenine

Table 5. Number of adverse gastrointestinal reactions

	By drug					By chemical characteristics				Total
	ASP	IND	DF	TRF	PIX	PRP[a]	ALY[b]	OXM[c]	CAL[d]	
Safety population	164	950	186	119	97	397	506	295	88	2802
Number of events	70	320	41	28	29	79	143	50	16	776
Abdominal Pain	22	59	9	2	4	20	34	15	3	168
Nausea/vomiting	14	40	3	1	2	7	14	2	1	84
Dyspepsia	8	20	3	1	1	7	17	4	2	63
Anorexia	2	19	1	4	0	4	8	1	0	39
Stomatitis	1	10	3	1	1	4	4	1	0	25
Diarrhea	0	8	2	1	0	3	3	0	0	17
Constipation	3	4	0	0	0	3	1	1	0	12
Other	3	10	3	0	2	1	6	2	0	27
Total	53	170	24	10	10	49	87	26	6	435

ASP, aspirin; IND, indomethacin; DF, diclofenac; TRF, tolfenamic acid; PIX. piroxicam; PRP, propionic acide; ALY, allyle acetate; OXM, oxicam; CAL, carboxylic acide

[a] Loxoprofen, alminoprofen, ketoprofen SR, tiaprofen acid, zaltoprofen, oxaprozin, naproxen, proanoprofen

[b] Amfenac, alclofenac, fenoprofen Ca, diclofenac SR, acemetacin, sulindac, proglumetacin maleate, nabumeton, etodolac, infomethacin facnesil

[c] Ampiroxicam, tenoxicam, lornoxicam, meloxicam

[d] Diflunisal, floctafenine

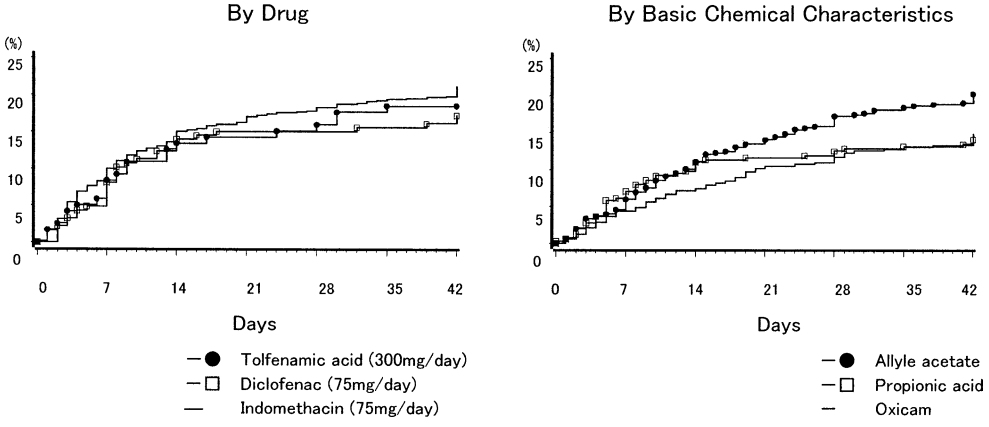

Fig. 1. Time to incidence of any adverse reactions

widely across the included studies [heterogeneity test: chi-square (df) = 25.72 (7), $P < 0.001$].

Number of adverse GI reactions

The number of adverse GI drug reactions classified according to symptom was determined from data on patients who had experienced adverse drug reactions (Table 5). A total of 2802 cases were included in the safety analysis, in which 776 events of adverse drug reactions occurred. Upper GI symptoms, i.e., abdominal pain (168 events), nausea/vomiting (67 events), and dyspepsia (63 events), were most common.

Kaplan–Meier curves for examination of the relationship between duration of treatment and occurrence of adverse drug reactions

For patients reporting adverse drug reactions, individual data on the adverse reaction were used to construct Kaplan–Meier curves from which the relationship between the occurrence of adverse drug reactions and the duration of treatment was examined. A Kaplan–Meier curve for the occurrence of any adverse drug reactions is shown in Fig. 1. Most withdrawals occurred during the first 3 weeks after administration, a finding consistent with the occurrence of any adverse drug reactions.

Covariate analysis

Eleven papers (22 treatment arms) in which detailed data on cases and covariates were available[18,20,23,24,26,36–38,40,42,43] for an analysis of the effects of covariates on the occurrence of adverse drug reactions are summarized in Table 6. The endpoints evaluated were any adverse drug reactions, all adverse GI drug reactions, and upper GI adverse drug reactions, and the covariates were gender and age. None of the comparisons showed significant heterogeneity across the 22 treatment arms. Analysis of the effects of gender showed that the incidence for each of the endpoints was significantly higher in females than in males. Summary odds ratios (OR) using the Mantel–Haenszel method were OR = 2.12 (95%

Table 6. Univariate risk factor analysis of incidence of adverse reactons

Endpoint	Number of study	Incidence/ proportion		Summary OR	95% CI		*P* value	Test of heterogeneity	
					Lower	Upper			
Sex		Male	Female						
Any adverse reaction	22	10.6	20.4	2.12	1.45	3.09	$P < 0.001$	$\chi^2(df) = 23.23\ (21)$	$P = 0.445$
Any digestive adverse reaction	22	6.8	13.1	2.01	1.27	3.18	$P = 0.003$	$\chi^2(df) = 26.78\ (21)$	$P = 0.178$
Upper GI side effect	22	5.5	10.2	1.89	1.13	3.15	$P = 0.015$	$\chi^2(df) = 24.89\ (21)$	$P = 0.252$
N		311	1558						
Age (years)		<59 years	60 years+						
Any adverse reaction	22	19.3	17.8	0.96	0.74	1.25	$P = 0.770$	$\chi^2(df) = 27.92\ (21)$	$P = 0.142$
Any digestive adverse reaction	22	13.2	10.4	0.82	0.59	1.12	$P = 0.212$	$\chi^2(df) = 19.97\ (21)$	$P = 0.523$
Upper GI side effect	22	10.4	7.6	0.74	0.52	1.07	$P = 0.107$	$\chi^2(df) = 18.94\ (21)$	$P = 0.589$
N		1252	617						

OR, odds ratio; CI, confidence interval; GI, gastrointestinal

CI, 1.45–3.09, $P < 0.001$) for any adverse drug reactions, OR = 2.01 (95% CI, 1.27–3.18, $P = 0.003$) for all GI adverse drug reactions, and OR = 1.89 (95% CI, 1.13–3.15, $P = 0.015$) for upper GI adverse drug reactions. Effects of age were examined by dividing the subjects into those younger than 60 years old and those aged 60 years or older. Combined OR for the three endpoints were 0.96 (95% CI, 0.74–1.25, $P = 0.770$; any adverse drug reactions), 0.82 (95% CI, 0.59–1.12, $P = 0.212$; all GI adverse drug reactions), and 0.74 (95% CI, 0.52–1.07, $P = 0.107$; upper GI adverse drug reactions), thus showing no evidence of the effects of age.

Discussion

Comprehensive safety evaluations of drugs have recently been discussed in reviews and guidelines.[49,50] It has been suggested that meta-analysis is a statistically useful method for comprehensive analyses of safety. Indeed, this method of analysis has been increasingly applied to the safety evaluation of drugs.[7,51–53] In Japan, however, only a few cases applying meta-analysis to safety evaluation have been reported, and this is the first study that has attempted to evaluate the safety of NSAIDs.

Treatment with NSAIDs may be limited by the poor tolerability of this class of drugs, which often leads to switching to relatively safe but less effective drugs, lowering of dosages, and concomitant prescribing of GI remedies.[54] However, because the doses of NSAIDs are relatively lower compared to Europe and the United States, switching to other drugs or lowering dosages may lead to the further reduction of effectiveness of these NSAIDs. The evidence on the concomitant use of GI remedies is variable and controversial, and this would include prostaglandin preparations for the replacement of NSAID-related decreases in prostaglandin, acid secretion-inhibiting drugs, and mucosa-protecting drugs. Prostaglandin preparations are effective in preventing gastric ulcer and duodenal ulcer but are often associated with toxic effects such as diarrhea.[54] H_2-receptor antagonists are effective for duodenal ulcer but do not show a preventive effect for gastric ulcer.[55] It has also been suggested that, because antacids and H_2-receptor antagonists are used for the improvement of subjective symptoms, they may facilitate the occurrence of more serious complications such as hemorrhage and perforating ulcer.[56] Proton pump inhibitors[57] are highly effective in preventing recurrence of NSAID-related ulcers, although they are associated with adverse events such as headache and arthralgia, and prophylactic use of these drugs is not covered by the current health insurance system. Thus, concomitant treatment with GI remedies is effective in preventing gastroduodenal ulcer, but no standard dosing regimen has been established. A well-tolerated drug infrequently associated with gastric mucosa damage, the most toxicologically significant adverse reaction to NSAIDs, would be ideal. Such characteristics are seen with cyclooxygenase-2 (COX-2)-specific inhibitors that have recently been approved in Europe and the United States. These new drugs have not yet been approved in Japan.

In the analyses of the cumulative incidence of any adverse reaction and any digestive event, analysis based on individual drugs seems to indicate a higher incidence compared to analysis of the basic chemical characteristics, although this cannot be statistically tested. A possible explanation may be that most of the drugs in which drug-level analysis was possible were in fact the standard control drugs recommended by the guidelines[17] and so they are rather old drugs. Data for drugs analyzed by basic chemical characteristics, on the other hand, were taken mainly from New Drug Application (NDA) trials. Because these drugs were newer than the standard controls, they seemed to have a better efficacy and safety profile, although there were no studies to statistically prove this hypothesis in Japan.

Doses and clinical trial treatment periods of NSAIDs approved in Japan are different from those in the United States and Europe, so a direct comparison of cumulative incidence of adverse reaction induced by NSAIDs is not

possible. However, as shown in the Kaplan–Meier curves constructed for the occurrence of adverse drug reactions, most adverse drug reactions occurred as early as 2–3 weeks after administration, a pattern of occurrence similar to that seen in a U.S. study performed by Bensen et al.[7]

There are only a few double-blind, placebo-controlled studies of NSAIDs available in Japan, so it is not fully known what level of adverse events would occur with placebo. However, placebo-controlled studies of NSAIDs administered to patients with osteoarthritis or lumbago for 2 weeks are available.[58–61] The combined incidence of any adverse drug reactions for the placebo arm in this study was 5.9% (95% CI, 3.2%–8.5%) and the incidence of upper GI adverse drug reactions was 5.6% (95% CI, 2.9%–8.3%). Although the difference in duration of treatment and target diseases makes it impossible to compare the results directly to this RA study, these findings at least suggest that the incidence of adverse drug reactions determined in this study is at a clinically meaningful level.

Analysis of the effects of covariates showed that the risk of any adverse drug reactions and GI adverse drug reactions was significantly higher in females. Bensen et al.[7] compared the occurrence of upper GI adverse drug reactions between males and females and showed a hazard ratio of 1.43 (95% CI, 1.14%–1.80%), with the risk being significantly higher in females, a finding consistent with the results of this study. Recently, Yamanaka et al.[3] reported that females experience more GI symptoms than males in their cross-cultural survey. However, no study exists to discuss a hypothesis that there is a sex difference of the incidence of GI symptoms in patients with NSAID treatment. When effects of age were examined in this study, the risk of any adverse drug reactions and adverse GI drug reactions was not significantly different between subjects younger than 60 years and those aged 60 years or older. This finding was also consistent with the results reported by Bensen et al.[7] They have reported that previous history and disease activity of GI ulcers are risk factors for the occurrence of upper GI adverse drug reactions. In this study, however, detailed data suitable for such an examination as well as rheumatic symptoms of the patients could not be obtained.

The results of this study are subject to limitations of study design as well as limitations of the evidence coming from all the included studies. First, publication bias must be taken into consideration for meta-analyses. Studies that do not show effective clinical results are often not published; thus, there is generally a concern that a meta-analysis of efficacy would overestimate the results. However, this study is intended to evaluate safety, and although the presence of publication bias (fewer publications of study results for drugs whose development was terminated because of safety concerns) is certainly possible, the bias would be in a conservative direction i.e., NSAID safety would be overestimated. A second limitation is related to the Good Clinical Practice guidelines (GCP). All papers examined in this study were published before the current GCP became effective. The current GCP requires more strict evaluation of adverse drug reactions: an adverse event is defined as any medical event occurring in patients treated with the study drug, and adverse events related to drugs are regarded as adverse drug reactions. It is generally recognized that the requirements for adverse drug reaction reporting in clinical studies under the former GCP are less strict than those specified under the current GCP, which again suggests that the NSAID safety results from this study may be overestimated. A third limitation is related to generalization of the results. All studies examined are double-blind, controlled studies. Therefore, the study populations and therapeutic policies in these studies do not represent real clinical practice, and some of the results are not suitable for extrapolation. Last, it should be kept in mind that because upper GI symptoms have been found to be poor indicators of severe events such as perforations ulcers, and bleeds (PUBs)[9,10,14] the clinical significance of the incidence of adverse reactions in this study does not directly imply the subsequent risk of more severe events.

The objective of this study was to systematically analyze the results of clinical studies of NSAIDs for the purpose of evaluating the risk of adverse reactions to NSAIDs in Japan. It was found that, although the incidence of adverse drug reactions varied according to the type of NSAIDs, the risk of adverse drug reactions was at a clinically significant level in Japan. The pattern of occurrence was similar to that found in Europe and the United States. Adverse drug reactions began to occur immediately after administration, a finding that suggests close monitoring of patients treated with these drugs is needed.

References

1. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guideline for the management of rheumatoid arthritis. Arthritis Rheum 1996;39:713–22.
2. Simon LS, Yocum D. New and future drug therapies for rheumatoid arthritis. Rheumatology 2000;39(suppl 1):36–42.
3. Yamanaka H, Singh G, Matsuda Y, Tanaka E, Urano K, Nakajima H, et al. Cross-sectional analysis of NSAID-related GI injury in patients with RA: a study using GI score questionnaire (in Japanese). Ensyo/Saisei 2002;22:61–6.
4. Saito T. Merits and demerits of NSAIDs (in Japanese). Igaku No Ayumi 1997;189:621–5.
5. Kawai S. NSAIDs to patients with rheumatoid arthritis and their side-effects (in Japanese). Chiryou Gaku 1999;33:851–5.
6. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious GI complications in patients with rheumatoid arthritis receiving nonsteroidal antiinflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241–9.
7. Bensen WG, Zhao SZ, Burke TA, Zabinski RA, Makuch RW, Maurath CJ, et al. Upper GI tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. J Rheumatol 2000;27:1876–83.
8. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. GI toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis – the CLASS Study: a randomized controlled trial. JAMA 2000;284:1247–55.
9. Spencer-Green G, Spencer-Green E. Nonsteroidal therapy of rheumatoid arthritis and osteoarthritis: how physicians manage treatment failure. J Rheumatol 1998;25:2088–93.
10. Singh G, Ramey DR. NSAID induced GI complications: the ARAMIS perspective – 1997: Arthritis, Rheumatism, and Aging Medical Information System. J Rheumatol Suppl 1998;51:9–16.

11. Wolfe F, Hawley DJ. The comparative risk and predictors of adverse GI events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. J Rheumatol 2000;27: 1668–73.
12. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious GI complications related to use of non-steroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991;115:787–96.
13. Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, et al. Variability in risk of GI complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996;312:1563–6.
14. Shiokawa Y, Nobunaga M, Saito T, Asaki S, Ogawa Y. Epidemiologic study on upper GI lesions induced by non-steroidal anti-inflammatory drugs (in Japanese). Ryumachi 1991;31:554–71.
15. Saito T, Hasegawa M. NSAID induced GI toxicity: survey for RA patients of Japan Rheumatism Friendship Association (in Japanese). Ryumachi 2001;41:375.
16. Yamanaka H, Singh G, Matsuda Y. Planning of J-ARAMIS for RA patients in Japan (in Japanese). Ryumachi 2001;41:521.
17. Working group of clinical evaluation methodology for analgesic and anti-inflammatory drugs. Guidelines for Clinical Evaluation of Analgesic and Anti-inflammatory Drugs (revised) (in Japanese). Iyakuhin Kenkyu 1985;16:544–53.
18. Shiokawa Y, Okada T, Yoshino R, Naeda A, Yoshioka Y, Nagaya I, et al. A multi-center, double blind, controlled study of renbufen on rheumatoid arthritis: a long-term study compared with aspirin (in Japanese). Igaku No Ayumi 1978;104:614–38.
19. Shichikawa K, Iwao T, Ogawa R. Clinical evaluation of Diflunisal on rheumatoid arthritis (in Japanese). Ryumachi 1983;23:268–79.
20. Kageyama K, Kashiwazaki S, Shiokawa Y, Hayashi T, Fujimori I, Mizushima Y, et al. Clinical evaluation of Floctafenine on rheumatoid arthritis: a multi-center double blind controlled study compared to aspirin (in Japanese). Yakuri To Chiryo 1985;13:557–94.
21. Kawakami Y, Iwasaki Y, Fujimori I, Kato F, Hayashi H, Mano J, et al. Clinical evaluation of GEA6414 on rheumatoid arthritis: a double blind study compared to indomethacin (in Japanese). Kiso To Rinsho 1981;15:445–72.
22. Miura T, Inagaki Y, Muramoto K, Ito K, Inoue K, Otani N, et al. Clinical evaluation of tolfenamic acid on rheumatoid arthritis: a double blind study compared to diclofenac (in Japanese). Igaku To Yakugaku 1986;16:281–97.
23. Nishioka H, Tanaka T, Nobunaga T. Clinical evaluation of EB-382 (Alminoprofen) on rheumatoid arthritis (in Japanese). Ryumachi 1986;26:210–20.
24. Shiokawa Y, Kumeno K, Warabi H, Homma M, Abe T, Kosaka S, et al. Evaluation of clinical usefulness of Amfenac Sodium (AHR-5850) on rheumatoid arthritis: a multi-center, double blind, randomized study compared to indomethacin (in Japanese). Kiso To Rinsyo 1982;16:509–30.
25. Yoshida H, Nobunaga T, Ogawa R. A double blind controlled study of SR-318 in rheumatoid arthritis (in Japanese). Yumachi 1988;28:188–98.
26. Shichikawa K, Nagaya I, Ogawa R. Clinical evaluation of Sulindac for rheumatoid arthritis (in Japanese). Yumachi 1979;19:164–83.
27. Fujimoti I, Shiokawa Y, Shichikawa Y, Kageyama T, Mizushima Y, Sato Y. Clinical evaluation double blind study) of K-708 (Acemetacin) in rheumatoid arthritis (in Japanese). Yakuri To Chiryo 1981;9:281–301.
28. Saito T, Iwasaki Y, Nobunaga T. Clinical evaluation of proglumetacin maleate on rheumatoid arthritis: a multi-center, double blind, randomized study (in Japanese). Ryumachi 1986;26: 377–89.
29. Shiokawa Y, Miyamoto M, Hirose T, Sugawara S, Warabi H, Nagaya I, et al. Clinical evaluation of E-0710 on rheumatoid arthritis: a multi-center, double blind, randomized study compared to indomethacin (in Japanese). Shinryo To Shinyaku 1989;26:63–94.
30. Nobunaga T, Sugioka Y, Aoki T. Clinical evaluation of indomethacin farnesil soft capsule on rheumatoid arthritis: a multi-center, double blind, randomized study compared to indomethacin farnesil hard capsule (in Japanese). Shinryo To Shinyaku 1993;30: 29–51.
31. Homma M, Kuriyama K, Kashiwazaki S, Yoshizawa H, Nagaya I, Sugawara S, et al. Clinical evaluation of RAK-591 in rheumatoid arthritis: double blind study in comparison with indomethacin (in Japanese). Rinsyo Iyaku 1991;7:123–44.
32. Nagaya I, Homma M. A controlled clinical trial of ketoprofen in rheumatoid arthritis: comparison with aspirin (in Japanese). Rinsyo Yakuri 1978;9:369–84.
33. Shichikawa K, Takasugi K, Ogawa Y. Clinical evaluation of Fenoprofen in rheumatoid arthritis (in Japanese). Ryumachi 1981;21:351–60.
34. Igarashi M, Ogawa R, Nobunaga T. Clinical evaluation of CS-600 (loxoprofen sodium) in rheumatoid arthritis (in Japanese). Ryumachi 1985;25:61–72.
35. Nishioka K, Tanaka T, Nobunaga T. Clinical evaluation of EB-382 (Alminoprofen) in rheumatoid arthritis (in Japanese). Ryumachi 1986;26:210–20.
36. Warabi H, Ogawa Y, Azuma T. Clinical evaluation of RPY-001 in rheumatoid arthritis (in Japanese). Ryumachi 1989;29:303–17.
37. Suzuki K, Mizushima Y, Kanno T, Tanaka M, Fujimori I, Kouno M, et al. Clinical evaluation of Tiaprofenic acid in rheumatoid arthritis: a multi-center, double blind, randomized study compared with indomethacin (in Japanese). Rinsyo To Kenkyu 1982;59:309–23.
38. Katsu M, Kosaka S, Ikari T, Honda M, Ashizawa K, Uetoku Y, et al. Clinical evaluation of naproxen in rheumatoid arthritis by double blind method (in Japanese). Rinsyo To Kenkyu 1978;55:251–74.
39. Shichikawa K, Igawashi M, Ogawa Y. Clinical evaluation of Pranoprofen on rheumatoid arthritis (in Japanese). Ryumachi 1979;19:379–95.
40. Yoshizawa H, Ogawa Y, Azuma T. Clinical evaluation of Pranoprofen on rheumatoid arthritis (in Japanese). Ryumachi 1991;31:127–38.
41. Shiokawa Y, Shichikawa K, Homma M, Kageyama T, Sakuma A, Mizushima Y. Clinical evaluation of oxaprozin on rheumatoid arthritis: a double blind comparative study with diclofenac as a control (in Japanese). Igaku No Ayumi 1984;130:386–403.
42. Shichikawa K, Abe T, Azuma T, Ogawa Y. A multi-center, double blind, randomized, controlled study for clinical evaluation of Pranoprofen on rheumatoid arthritis (in Japanese). Ryumachi 1980;20:220–8.
43. Tosu T, Nobunaga T, Iwasaki Y. Clinical evaluation of Tenoxicam on rheumatoid arthritis (in Japanese). Ryumachi 1984;24:295–308.
44. Sugawara S, Yamamoto M, Yamauchi Y, Fujimaki E, Yoshizawa H, Torikai M, et al. A multi-center, double blind, randomized, controlled study for clinical evaluation of Pranoprofen compared with piroxicam on rheumatoid arthritis (in Japanese). Rinsyo To Kenkyu 1991;68:331–42.
45. Mizushima Y, Ichikawa Y, Kashiwazaki S, Sugawara S, Nagaya I, Hirohata K, et al. Clinical evaluation of TS-110 against rheumatoid arthritis: double blind comparative study using indomethacin as a control (in Japanese). Ensyo 1997;17:421–43.
46. Mizushima Y, Hoshi K, Kawai S, Sugawara S, Tojo T, Takasaki Y, et al. Clinical evaluation of UHAC62 (Meloxicam) capsule in rheumatoid arthritis: a phase III double blind study vs. Piroxicam capsule (in Japanese). Kiso To Rinsyo 1997;31:1115–66.
47. Sano O, Tsubouchi Y, Kondo M. Nonsteroidal anti-inflammatory drugs (in Japanese). Rinsyo To Kenkyu 1999;76:1676–81.
48. Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare. Adverse drug reaction terminology (in Japanese). Ministry of Health and Welfare, Tokyo, 1993.
49. Fairweather WR: Integrated safety analysis: statistical issues in the assessment of safety in clinical trials, Drug Inf J 1996;33:211–24.
50. Enas GG, Goldstein DJ. Defining, monitoring and combining safety information in clinical trial. Stat Med 1995;14:1099–111.
51. Riedemann PJ, Bersinic S, Cuddy LJ, Torrance GW, Tugwell PX. A study to determine the efficacy and safety of tenoxicam versus poroxicam, diclofenac and indomethacin in patients with osteoarthritis: a meta-analysis. J Rheumatol 1993;20:2095–103.
52. Schoenfeld P. GI safety profile of meloxicam: a meta-analysis and systematic review of randomized controlled trials: Am J Med 1999;107(6A):49S–54S.
53. Huang JQ, Sridhar S, Hunt RH. GI safety profile of nabumetone: a meta analysis: am J Med 1999;107(6A):55S–64S.
54. Miyake K, Sakamoto C. Treatment of NSAIDs induced ulcer (in Japanese). Prog Med 1999;19:2060–64.

55. Lanza FL. Prophylaxis against nonsteroidal anti-inflammatory drug-associated ulcer and erosions: a commentary on the new data: Am J Gastroenterol 1996;103(3A):75S–8S.
56. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. GI tract complications of nonsteroidal anit-inflammatory drug treatment in rheumatoid arthritis. Arch Intern Med 1996;156:1530–6.
57. Curllen D, Bardhan KD. Primary gastroduodenal prophylaxis with omeprazole for nonsteroidal anti-inflammatory drug users. Aliment Pharmacol Ther 1998;12:135–40.
58. Shibano K, Mori M, Horiuchi Y, Asai T, Ando K, Sugawara S, et al. Clinical evaluation of tolfenamic acid in lumbago: a double blind, randomized, controlled study (in Japanese). Kiso To Rinsyo 1980;14:1469–79.
59. Yamashita B, Sakakita K, Hirasawa T, Hashimoto I. Clinical evaluation of nonsteroidal anti-inflammatory drug, GEA6414: a double blind, randomized, controlled study compared with aspirin and placebo (in Japanese). Kiso To Rinsyo 1980;14:4877–99.
60. Yamamoto M, Nakajima N, Kageyama T, Maezono M, Uchiyama S, Aoki T. Multi-clinic comparative study on efficacy of fenbufen in patients with lumbar pains due to spondylosis deformans (in Japanese). Yakuri To Chityo 1976;4:949–58.
61. Kageyama T, Igarashi M, Hayashi Y, Masuda M, Mikami R, Kawabata M. Clinical evaluation of pranoprofen in osteoarthritis: a multi-center, double blind, randomized study compared to indomethacin and placebo (in Japanese). Igaku No Ayumi 1979;119:188–211.