Risk factors of adverse drug reaction from non-steroidal anti-inflammatory drugs in Shanghai patients with arthropathy[1]

Wen SHI[2], Yong-ming WANG, Shao-li LI[3], Min YAN[3], Duan Li, Bin-yan CHEN, Neng-neng CHENG

Department of Pharmacology, School of Pharmacy, Fudan University, Shanghai 200032; [3]The Center for Drug Reevaluation and The Center for Adverse Drug Reaction Monitoring, State Food and Drug Administration, Beijing 100061, China

KEY WORDS non-steroidal anti-inflammatory drugs; adverse drug reaction; risk factors; retrospective studies; quality of life

ABSTRACT

AIM: The study was to screen the possible risk factors of adverse drug reaction (ADR) induced by non-steroidal anti-inflammatory drugs (NSAIDs) in Shanghai patients with arthropathy. **METHODS:** The subjects were randomly selected from a database of outpatients with arthropathy from 9 main hospitals in Shanghai. A door to door retrospective epidemiological survey was used to collect demographic information about the patients, both individual and familial. This included data on their medical histories, lifestyle and dietary habits, history of smoking and alcohol consumption, history of drug therapy, quality of life (QOL) prior to NSAIDs intake, history of NSAIDs therapy and its ADR events, *etc.* Descriptive statistical methods and univariate analysis were also used to identify possible risk factors for ADRs induced by NSAIDs. **RESULTS:** Of the 1002 patients surveyed, the average length of NSAIDs intake was 2 years. ADR incidence from different NSAIDs was high, in a range from 46.7 %-66.2 %. In general, the candidate risk factors for ADRs were different for each NSAID. Each of the candidate risk factors were defined and studied in order to evaluate its role in the determination of ADRs from NSAIDs. "Family history of ADRs caused by NSAIDs" was found to be a significant risk factor for the four commonly used NSAIDs: meloxicam, diclofenac, nimesulide, and nabumetone. **CONCLUSION:** A retrospective epidemiological survey was useful in detecting the risk factors for ADRs caused by NSAIDs. The study found that different NSAIDs might have different risk factors and that there is no single risk factor universally applicable to all NSAIDs.

INTRODUCTION

In clinical practice, adverse drug reactions (ADRs) often follow the successful treatment of arthropathy by non-steroidal anti-inflammatory drugs (NSAIDs). To decrease or even avoid the high probability of ADR occurrence from NSAIDS whose incidence was above 30 % for long term intake[1], many new types of NSAIDs like Cox-2 selective/specific inhibitors were developed. These drugs were clinically proven satisfactory for decreasing gastro-intestinal (GI) side effects, the most common ADR from NSAIDs[2,3]. However, Cox-2 inhibitors are not safe in all respects, a feature shared with

[1] The project was supported by The Center for Drug Reevaluation and The Center for Adverse Drug Reaction Monitoring, State Food and Drug Administration, China. Grant No BK-PJ-0301.

[2] Correspondence to Wen SHI. Phn 86-21-5423-7465. Fax 86-21-5491-0623. E-mail vivianshi2001@yahoo.com.cn

Received 2003-05-06 Accepted 2003-09-12

all traditional NSAIDs[4]. Different NSAIDs have different typical ADRs and the severity of these can also differ according to the patient's specific circumstances[1,5-10]. It should be possible, therefore, to develop some practical methods to minimize or even avoid ADRs by selecting the most suitable NSAID on an individual basis. The success in determining the risk factors for GI bleeding[11] helps to support the hypothesis that it might also be possible to identify the risk factors for overall ADR occurrence and then select the most suitable NSAID for each particular patient. In this study, we tried to obtain some indicators of ADR risks through a broad scan of many variables from the demographic data, use of NSAIDs, lifestyle, quality of life (QOL), *etc*.

MATERIALS AND METHODS

Study sample The subjects met all the following enrollment criteria:

1) Being a patient with one of the following diseases: osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or some other non-malignant arthropathy, according to the American College of Rheumotology standards.

2) Being a Shanghai resident (of either gender).

3) The patient began treatment with NSAIDs some time between 1996 January 1st and 2000 December 31st. Also included were patients with a history of NSAID treatment who renewed such treatment any time between 1996 January 1st and 2000 December 31st, with an interval of more than 6 months between the two NSAIDs applications.

4) All patients should have taken NSAIDs continuously or intermittently for at least 1 year.

5) If the patient was on NSAIDs intermittently, the combined therapy time should exceed more than half of the total observational period.

Concomitant diseases did not exclude patients from enrollment, but subjects with no detailed address information, no compliance with the investigation, who were older than 85 years, had memory disorders or personality disorders such as paranoia, deliria, schizophrenia, *etc*, were excluded.

Data collection and preparation The collection of survey data was limited to the period from 1996 January 1st to 2002 January 31st. Data were collected using the investigator-administrated Case Report Form (CRF) through door-to-door visits. Letters and phone calls were used to clarify any concerns about the recorded information on CRFs. Interviewers were all trained and examined to improve their level of understanding of the CRF questions.

Further more, they were all trained to be qualified in terms of good interview techniques and field survey bias control. Twenty percent of all completed CRFs were randomly selected for re-interview by other interviewers to double-check information reliability.

Data on CRFs were then keyed into the Access database and the data were double-checked by computer. If any abnormal deviation was identified, the suspected data was corrected by the study coordinator, data administrator and clinical specialists. In such cases, proper records, including reasons for the corrections, were made and signed. The database was locked when it was completed.

The retrospective epidemiological survey strictly followed ICH GCP guidelines. Each of the subjects was given a full explanation of what would be involved in the study and fully understood what the study was about. All subjects signed the consent form before they were enrolled in the study. The Ethic Committees of the nine involved hospitals approved the study protocol before the study started.

Data collected includes patient's demographic information, history of NSAIDs taken and associated ADRs, concomitant drug therapy, family and personal anamnesis, smoking and alcohol consumption history, lifestyle, dietary habits, mood, previous drug therapy, and QOL prior to NSAIDs therapy.

All recorded adverse events (AEs) appearing during the period of NSAIDs intake were comprehensively evaluated by the ADR evaluation group composed, of the researchers and professional rheumatologists. Cases were excluded only if the relationship analysis indicated that the AE was impossible or unrelated to NSAIDs, or after withdrawal of the suspected NSAIDs the AE symptoms increased in severity.

Statistical analysis SAS (Version 8.0) was used for all statistical analysis. Descriptive statistics of the measurement data were expressed as mean±SD and were used to interpret the overall use of NSAIDs. the R×C Chi-Square test was used to evaluate the enumeration data, such as gender, education, dosage details, *etc*. Wilcoxon's test was used to evaluate rank data, such as smoking, drinking alcohol, tea and coffee and other lifestyle traits, *etc*. as well as measurement data such as age, weight, blood pressure, medical payments, diseases course, *etc*. as many of the measurement data were not normal distributed. A logistic regression model

was used to determine the risk factors when all the variables were considered as a whole. A discriminatory function analysis was adopted for the determination of the discriminatory equation.

RESULTS

A total of 1002 patients were enrolled in the study, 230 (22.95 %) male, and 772 (77.05 %) female, with a mean age of 53.7±13.2 (9-84 a). The course of disease was 2517.4±2244.5 d. Among all the patients, 847 (84.5 %) were diagnosed with rheumatoid arthritis, 44 (4.4 %) with osteoarthritis, 57 (5.7 %) with psoriatic arthritis, 16 (1.6 %) with prolapsed lumbar intervertebral disc, and another 38 with other forms of arthopathies. Patients 980 (97.8 %) had at least one concomitant drug therapy during the observation period. All the patients had at least a one-year history of NSAIDs intake.

Diclofenac, ibuprofen, indomethacin, nimesulide, meloxicam, and nabumetone were found to be the top six orally taken NSAIDs among Shanghai patients with arthropathy. The incidences of ADR of these drugs were summarized in Tab 1. Diclofenac was particularly widely taken, with 926 (92.4 %) patients taking this NSAID among those in the survey. We also found that patients typically switched NSAIDs, with 834 (83.2 %) patients found to have switched NSAID (accounted by chemical names of drugs) at least once, for different reasons. Among these 834 patients, 301 (30.04 %) switched 2 NSAIDs, 230 (22.95 %) switched 3, 163 (16.27 %) switched 4, 110 (10.98 %) switched 5 and 30 (2.99 %) switched 6 or more. The main reasons for withdrawal and switching of NSAIDs were: in 248 (24.75 %) cases prescription changes, in 224 (22.36 %) cases ADR intolerance, 205 (20.46 %) thought the drugs were ineffective, 38 (3.79 %) thought they had recovered or their health condition had improved and 58 (5.79 %) were for other unknown reasons.

There were 504 (50.3 %) patients who suffered from ADRs from NSAIDs. Among these, 366 (36.5 %) patients suffered one ADR, 101 (10.1 %) patients suffered 2 ADRs and 37 (3.7 %) suffered 3 ADRs. Tab 2 shows the composition of different ADRs caused by NSAIDs and the number of patients who received therapy for the ADRs.

The risk factors of the ADRs varied widely among different NSAID subgroups. In total, 35 variables were found significant for the top 6 NSAIDs. No single variable was found to be universally applicable as a risk factor for all of the NSAIDs. Among the 35 variables, the "family history of ADR caused by NSAIDs" was the sole significant risk factor for the following commonly used NSAIDs: meloxicam, diclofenac, nimesulide and nabumetone. Other variables include "Compared to one year ago, how would you rate your health in general now?" (related to ADRs in diclofenac, ibuprofen and indomethacin), "Daily alcohol consumption" (related to ADRs in meloxicam, diclofenac and indomethacin),

Tab 1. The use of NSAIDs and incidence of ADR in Shanghai participants with arthropathy.

No	Generic name of NSAIDs	Case	No ADR/%*	ADR/%	Average dosage per day/mg	Average dosage duration/a$^{\Delta}$
1	Diclofenac	926	532(57.5)	394 (42.5)	99.2±77.0	2.00±0.38
2	Ibuprofen	447	255 (57.0)	144 (32.2)	740.7±352.1	2.01±0.37
3	Indomethacin	436	224 (51.4)	212 (48.6)	240.1±127.4	2.00±0.31
4	Nimesulide	266	147 (55.2)	119 (44.7)	198.5±67.7	2.05±0.35
5	Meloxicam	248	149 (60.1)	99 (39.9)	14.7±11.5	2.30±0.74
6	Nabumetone	145	96 (66.2)	49 (33.8)	988.2±421.9	1.98±0.14
7	Diclofenac+misoprostol	97	50 (56.7)	47 (48.5)	144.2±139.9	1.99±0.14
8	Sulindac	69	37 (53.6)	32 (46.4)	353.2±124.3	1.99±0.12
9	Acemetacin	53	28 (52.8)	25 (47.2)	107.3±50.5	2.13±0.52
10	Piroxicam	45	21 (46.7)	24 (53.3)	26.7±12.2	1.98±0.15
11	Oxaprozin	25	25 (56.0)	11 (44.0)	432.0±160.0	2.08±0.49
12	Acetylsalicylic acid	17	10 (58.8)	7 (41.2)	567.7±179.4	2.00±0.00

ADR data for which the number of cases was less than 10 were omitted.
* R×C Chi-square test, $^{\Delta}$Wilcoxon's test.

Tab 2. ADR events induced by NSAIDs.

No	Symptom	Case of ADR / %	Cases receiving therapy for ADR / %
1	Stomach discomfort	331 (33.0)	113 (34.1)
2	Stomach ache	92 (9.2)	44 (47.8)
3	Rash	90 (9.0)	15 (16.7)
4	Dizziness	89 (8.9)	29 (32.5)
5	Nausea	52 (5.2)	4 (7.7)
6	Vomiting	27 (2.7)	4 (7.7)
7	Distention	26 (2.6)	13 (50.0)
8	Clouded vision	25 (2.5)	1 (4.0)
9	Dyspepsia	23 (2.3)	1 (4.0)
10	Gastric bleeding	21 (2.1)	20 (95.2)
11	Acid belching	18 (1.8)	8 (44.4)
12	High blood pressure	18 (1.8)	8 (44.4)
13	Facial edema	17 (1.7)	1 (5.9)
14	Palpitation	17 (1.7)	1 (5.9)
15	Leucopoenia	16 (1.6)	8 (50.0)
16	Head ache	16 (1.6)	1 (6.3)
17	Renal function abnormality	16 (1.6)	7 (43.8)
18	Malaise	15 (1.5)	0 (0)
19	Diarrhea	14 (1.4)	2 (14.3)
20	Discomfort of hepatic region	13 (1.3)	4 (30.8)
21	Liver function abnormality	13 (1.3)	5 (38.5)
22	Low extremity edema	12 (1.2)	2 (16.7)
23	Constipation	10 (1.0)	1 (10.0)

ADR data for which the number of cases was less than 10 were omitted.

"Course of the disease" (related to ADRs in meloxicam, diclofenac and nabumetone), "Degree of personal care" (related to ADRs in diclofenac, nabumetone and nimesulide) and "Concomitant drug therapy" (related to ADRs in ibuprofen, nimesulide and indomethacin). The remaining 7 variables were significant in two of the six NSAIDs subgroups and the last 22 variables were significant for one out of the six NSAIDs subgroups (Tab 3.1-3.6. *R×C Chi-square test, the statistics is χ^2. $^{\Delta}$Wilcoxon's test, the statistics is Z)

Taken meloxicam for example, after comparison of identified risk factors between subjects with ADRs and those without ADRs, the contribution of these risk factors to the determination of ADRs indicated the following: the course of disease in the non-ADR group was significantly longer than that of ADR group; patients were prone to suffer from the ADRs of meloxicam when there is a family history of ADRs from NSAIDs; daily alcohol consumption was significantly higher in the non-ADR subgroup; if the patients felt that physical health and QOL could be impacted by stress, they were susceptible to ADRs; more patients in the non-ADR group were much more willing to negotiate conflicts with others, to accept irreversible setbacks, and to embrace challenges. (Tab 4.1-4.3. *R×C Chi-square test, the statistics is χ^2. $^{\Delta}$Wilcoxon's test, the statistics is Z)

DISCUSSION

This research is the first survey on ADRs from NSAIDs in China. The results show that the types of ADRs from NSAIDs in Shanghai patients with arthropathy were similar to those revealed by other published reports[1,5-10]. The incidence of ADRs from NSAIDs among Shanghai patients with chronic arthropathy was above 46 %. This may be due to the long-term use of NSAIDs and high frequency of concomitant drug therapy, including some traditional Chinese

Tab 3.1. Univariate analysis for scan of the risk factors of ADR caused by meloxicam. * R×C Chi-square test, $^{\Delta}$Wilcoxon's test.

No	Variables	Statistics	*P*
1	Course of disease$^{\Delta}$	-2.6512	0.00802
2	Family history of ADR caused by NSAIDs*	5.912	0.01503
3	Daily alcohol consumption$^{\Delta}$	-2.4191	0.01556
4	The ability to mitigate conflicts with others$^{\Delta}$	-2.2583	0.02393
5	Acceptability of irreversible setback$^{\Delta}$	-2.3685	0.01786
6	Whether physical heath and QOL are influenced by external stress*	6.2192	0.01264
7	Being interested in every challenge$^{\Delta}$	-2.4776	0.01323
8	The extent by which the stress from society can impact on life$^{\Delta}$	2.08321	0.03723
9	The extent by which the stress from health can impact on life$^{\Delta}$	-2.4412	0.01464

Tab 3.2. Univariate analysis for scan of the risk factors of ADR caused by diclofenac.

No	Variables	Statistics	*P*
1	Daily amount of diclofenac intake$^{\Delta}$	-2.2095	0.02710
2	Family income$^{\Delta}$	-2.0909	0.03653
3	The level of reimbursement for medical expense$^{\Delta}$	14.0033	0.01559
4	Family history of ADR caused by NSAIDs*	18.4793	0.00002
5	Daily alcohol consumption$^{\Delta}$	2.2316	0.02564
6	Concomitant use of cigarettes and alcohols*	-2.3462	0.01897
7	Family anamnesis*	7.12001	0.00762
8	Course of the disease$^{\Delta}$	2.1199	0.03401
9	The ability to mitigate conflicts with others$^{\Delta}$	1.90673	0.05655
10	Degree of personal care*	1.98768	0.04685
11	On diet*	5.28984	0.02145
12	Salty food*	6.97575	0.03057
13	Compared to six months ago, how would you rate your health in general now?$^{\Delta}$	2.26170	0.02372
14	How much bodily pain have you had during the past 4 weeks?$^{\Delta}$	1.99527	0.04601
15	How much of the time during the past 4 weeks before NSAIDs therapy have you been very nervous?$^{\Delta}$	-2.2295	0.02578
16	How much of the time during the past 4 weeks before NSAIDs therapy have you felt downhearted and depressed?$^{\Delta}$	-0.90697	0.03205
17	Have you ever suffered from anxiety, which impact your life*	5.4301	0.01979

Tab 3.3. Univariate analysis for scan of the risk factors of ADR caused by ibuprofen.

No	Variables	Statistics	*P*
1	Concomitant drug therapy*	10.1381	0.00145
2	Family anamnesis*	6.8068	0.00908
3	When to take ibuprofen every day$^{\Delta}$	12.7738	0.01244
4	Compared to six months ago, how would you rate your health in general now?$^{\Delta}$	4.32581	0.00002
5	How much of the time during the past 4 weeks before NSAIDs therapy have you been very nervous?$^{\Delta}$	-2.92217	0.00348
6	How much of the time during the past 4 weeks before NSAIDs therapy did you feel worn out$^{\Delta}$	-2.57949	0.00989
7	Have you ever suffered from a feeling of hopeless, which impact your life*	10.2987	0.00133
8	Have you ever suffered from a feeling of loss of control, which impact your life *	5.8082	0.01595
9	Have you ever been hostile to others, which impact your life *	4.8897	0.02702

Tab 3.4. Univariate analysis for scan of the risk factors of ADR caused by nabumetone.

No	Variables	Statistics	*P*
1	Course of disease$^{\Delta}$	-2.3403	0.01927
2	Family income$^{\Delta}$	1.9663	0.04927
3	Family history of ADR caused by NSAIDs*	8.21776	0.00415
4	Degree of personal care$^{\Delta}$	2.66757	0.00764
5	Consumption of coffee$^{\Delta}$	2.21256	0.02693
6	Principle component derived from Category 5 in SF-36 form$^{\Delta}$	-2.07055	0.03840
7	Being interested in every challenge$^{\Delta}$	2.44859	0.01434
8	Being self-fulfilled$^{\Delta}$	2.01878	0.04351

Tab 3.5. Univariate analysis for scan of the risk factors of ADR caused by nimesulide.

No	Variables	Statistics	*P*
1	Concomitant drug therapy*	8.48039	0.00359
2	Family history of ADR caused by NSAIDs*	4.48109	0.03427
3	Degree of personal care$^{\Delta}$	-2.2855	0.02228
4	How much of the time during the past 4 weeks before NSAIDs therapy did you feel tired$^{\Delta}$	-2.10328	0.03544
5	The extent by which the stress from health can impact on life$^{\Delta}$	-2.11897	0.03409
6	Have you ever suffered from depression, which impact your life*	8.30511	0.00395

Tab 3.6. Univariate analysis for scan of the risk factors of ADR caused by indomethacin.

No	Variables	Statistics	*P*
1	Daily indomethacin consumption$^{\Delta}$	8.48039	0.00359
2	Concomitant drug therapy*	4.48109	0.03427
3	History of alcoholism$^{\Delta}$	-2.2855	0.02228
4	Daily alcohol consumption$^{\Delta}$	-2.10328	0.03544
5	Compared to six months ago, how would you rate your health in general now? $^{\Delta}$	-2.11897	0.03409
6	Whether physical heath and quality of life are influenced by external stress$^{\Delta}$	8.30511	0.00395

Tab 4.1. The differences in risk factors between ADR participants and non-ADR participants in meloxicam subgroup.

Risk factors	No ADR				ADR			
Course of disease$^{\Delta}$ / a	8.30±7.44				6.78±6.26			
Family history of ADR caused by NSAIDs* / %	No 126 (86.9)		Yes 19 (13.1)		No 46 (73.02)		Yes 17 (26.98)	
Daily alcohol consumption$^{\Delta}$ / mL	1.23±2.70				0.51±1.66			
The ability to negotiate the conflicts with others$^{\Delta}$ / %	Never 4 (2.76)	Sometimes 17 (11.72)	Usually 45 (31.03)	Everyday 79 (54.48)	Never 0 (0.0)	Sometimes 13 (20.63)	Usually 28 (44.44)	Everyday 22 (34.92)
Acceptability of irreversible setback$^{\Delta}$ / %	Never 9 (6.21)	Sometimes 11 (7.59)	Usually 44 (30.44)	Everyday 81 (55.86)	Never 7 (11.11)	Sometimes 5 (7.94)	Usually 27 (42.86)	Everyday 24 (38.10)
Whether physical health and QOL be influenced by stress* / %	Yes 35 (24.14)		No 110 (75.86)		Yes 26 (41.27)		No 37 (58.73)	
Being interested in every challenge$^{\Delta}$ / %	Never 8 (5.52)	Sometimes 27 (18.62)	Usually 43 (29.66)	Everyday 67 (46.21)	Never 4 (6.35)	Sometimes 17 (26.98)	Usually 26 (41.27)	Everyday 16 (25.40)

medicines, methotrexate, azathioprine and other drugs used to treat gastric and cardiovascular diseases, which would facilitate the occurrence of ADRs. Among all the ADRs induced by NSAIDs, gastric disorder such as stomach discomfort, epigastralgia, vomiting, nausea and belching were most common. Kidney function

Tab 4.2. The extent by which the stress from society can impact on life.[A]

	1	2	3	4	5	6	7	8	9	Total
Non-ADR / %	103 (71.1)	1 (0.7)	3 (2.1)	3 (2.1)	3 (2.1)	3 (2.1)	5 (3.5)	15 (10.3)	9 (6.2)	145 (100)
ADR / %	34 (54.0)	3 (4.8)	3 (4.8)	2 (3.2)	2 (3.2)	1 (1.6)	6 (9.5)	5 (7.9)	7 (11.1)	63 (100)
Total	137	4	6	5	5	4	11	20	16	208

Tab 4.3. The extent by which the stress from health issue can impact on life.[A]

	1	2	3	4	5	6	7	8	9	10	Total
Non-ADR / %	3 (2.1)	10 (6.9)	10 (6.9)	10 (6.9)	13 (9.0)	10 (6.9)	14 (9.7)	18 (12.4)	13 (9.0)	44 (30.3)	145 (100)
ADR / %	5 (7.9)	7 (11.1)	6 (9.5)	8 (12.7)	4 (6.4)	5 (7.9)	4 (6.4)	6 (9.5)	5 (7.9)	13 (20.1)	63 (100)
Total	8	17	16	18	17	15	18	24	18	57	208

Both in Tab 4.2 and Tab 4.3, 1 = minimum stress, 2-3 = mild stress, 4-6 = moderate stress, 7-8 = severe stress, 9-10 = maximum stress. Patient who was ranked as 1 would be most sensitive to stress from society or from health problems. Participants ranked as 10 were most resistant to such stress.

disorder, blood pressure increase, central nervous system disorders and hematological abnormalities were also observed.

Diclofenac was the most widely used NSAID among Shanghai patients with arthropathy. Therefore the ADRs from diclofenac are more relevant to patients overall. The addition of some mucosa protecting agent, such as misoprostol, has been recommended as a way to decrease the occurrence of GI bleeding, according to another report[12]. However, this study found that the total incidence of ADRs between diclofenac only and diclofenac with misoprostol are similar, $P>0.05$. These data indicated that for long-term use, the concomitant use of a mucosa protect agent did not necessarily improve the overall safety of diclofenac. A pharmacoeconomics study shows that the cost incurred from GI ADRs by NSAIDs were about US$150 million per year while that of acute renal toxicity induced by NSAIDs was around US$1.16 billion per year, although the ADR of GI was most common[13]. John *et al*[14] reported that the burden of illness resulting from NSAID-related chronic heart failure in elderly patients might exceed that resulting from gastrointestinal tract damage. These alerted us to the need for a comprehensive evaluation on ADRs from NSAIDs, rather than one focusing on GI toxicity alone.

Through univariate analysis we found that different NSAID had different risk factors, which might partly be due to the difference in the nature of each individual NSAID[15-17], and partly due to the limited number of enrolled patients. Our pilot statistical analysis, considering all the NSAIDs as a whole, could not find a significant difference in any of the variables between patients with ADRs and those without any ADR. We postulated that the difference in nature between each individual NSAID, which was unknown, might lead to the negative results in the pilot statistical analysis. Further, a single risk factor might play a different role in determining the occurrence of ADRs in different NSAIDs. In order to refine the analysis, therefore, all the collected data was stratified by NSAID-subgroup to evaluate ADRs on an individual NSAID basis, 35 variables were then found as candidate risk factors for ADRs from NSAIDs.

Although, some of these risk factors were statistically significant, further clinical review is required to see if they are applicable to clinical practice. For example, one would hypothesize that the longer the course of disease, the more NSAIDs would be taken and the more ADRs would occur. However, this hypothesis could be wrong, since patients might accumulate experiences in dealing with ADRs, and this experience could itself contribute to diminishing ADRs from NSAIDs. This was strongly suggested by our results for the meloxicam

subgroup, where a significantly shorter course of disease was shown among those with ADRs than those without.

Another example of a statistically significant result of potential clinical relevance was the finding that showing patients who were resistant to psychological stress from life and health issues were less susceptible to ADRs than those who were less resistant. One further example, the study results from Tab 4.2 and Tab 4.3 show opposite trends. In all such cases clinical evaluations of the risk factors remain critical.

For risk factors where no clinical meaning is evident, however, it may be both possible and useful to conduct a purely statistical investigation through multivariate analysis and then formulate a predictive model of ADR occurrences for each individual NSAID.

The variable "The family history of ADR caused by NSAIDs" was found significant and a general indicator for predicting ADR occurrences from the 4 most commonly used NSAIDs: meloxicam, diclofenac, nimesulide and nabumetone. For example, for patients taking meloxicam, 27 % of those suffering ADRs had a family history of ADRs from NSAIDs, while 19 % of those without meloxican-related ADRs had a family history of ADRs from NSAIDs, $P<0.05$. Another variable, "The daily alcohol consumption" might also have some impact on ADRs from meloxicam according to the study. Alcohol might disrupt the stomach mucus layer or increase the burden of the liver in terms of alcohol metabolism which in turn contributes to inducing ADRs from meloxicam[18] .

The WHO SF-36 QOL questionnaire and parts of the WHO QOL-100 questionnaire were introduced into the CRF for this survey. Using the meloxicam subgroup as an example once again, the variable "the ability to negotiate conflicts with others", "the acceptance of irreversible setbacks," "whether physical health and quality of life is influenced by stress;" and "being interested in every challenge" were the 4 independent risk factors for ADRs from meloxicam. As the validity and reliability of these, questionaries have been verified for assessing the QOL status of patients with arthropathy [19-21] , these variables (risk factors) have clinical implications.

Risk factor models for NSAIDs associated with gastropathy were constructed[3]. These models should be helpful to clinicians in predicting possible GI toxicity when they prescribe NSAIDs. These results prompt us to hypothesize that if more source materials were available and more risk factors were identified, we could establish models to predict the overall occurrences of ADRs induced by NSAIDs which could be more valuable to clinical practice. We have done some work in scanning the risk factors for ADRs from NSAIDs as introduced in this article. Further studies designed to obtain more information on ADRs from NSAIDs, using the same methods, could be conducted so that various ADR predicting models for NSAIDs could be constructed to help clinicians better manage ADRs from NSAIDs in their future clinical practice.

In conclusion, the survey found diclofenac, ibuprofen, indomethacin, nimesulide, meloxicam, and nabumetone were the top six orally taken NSAIDs among Shanghai patients with arthropathy. The average length of NSAIDs intake was 2 years and ADR incidence was high, from 46.7 %-66.2 %. The risk factors for ADRs differed between NSAIDs. "Family history of ADRs caused by NSAIDs" was found to be a significant risk factor for the four commonly used NSAIDs, which were meloxicam, diclofenac, nimesulide and nabumetone. The risk factors identified by statistical scans should be reviewed together with clinical practice to determine their clinical practicality.

ACKNOWLEDGEMENTS We thank the participating rheumatologists in the main 9 hospitals in Shanghai for their valuable cooperation.

REFERENCES

1 Marie R, Griffin MD. Epidemiology of non-steroidal anti-inflammatory drug-associated gastrointestinal injury. Am J Med 1998; 104: 23-8.
2 Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, *et al*. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison. Lancet 1999; 354: 2106-11.
3 Anna JM, David PF. Rofecoxib, a review of its use in the management of osteoarthritis, acute pain and rheumatoid arthritis. Drugs 2001; 61: 833-65.
4 Ahmad SR, Kortepeter C, Brinker A. Renal failure associated with the use of celecoxib and rofecoxib. Drug Safety 2002; 25: 537-44.
5 Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. Am J Med 1999; 106: 13-23.
6 Schafer AL. Effects of non-steroidal anti-inflammatory drugs on platelet function and systemic hemostasis. J Clin Pharmacol 1995; 35: 209-19.
7 Johnson AG, Nguyen TV, Day RO. Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994; 21: 289-300.
8 Heerdink ER. NSAIDs associated with increased risk of

congestive heart failure in elderly patients taking diuretics Arch Interm Med 1998; 158: 1108-12.

9 Buchanan W, Kean W. Rare side effects of non-steroidal anti-inflammatory drugs. In: Non-steroidal anti-inflammatory drugs, mechanisms and clinical uses. Lewis A, Furst D, editors. New York (NY): Marcel Dekker; 1994. p 217-43.

10 Proscott LF. The hepatotoxicity of non-steroidal anti-inflammatory drugs. In: Side-effects of anti-inflammatory drugs. Rainsford KD, Velo GP, editors. Lancaster (UK): Kluwer Academic; 1992. p 176-87.

11 Fries JF, Williams CA, Bloch DA, Michel BA. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. Am J Med 1991; 91: 213-22.

12 Silverstein FE, Graham DY, Senior JR. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving non-steroidal anti-inflammatory drugs: a randomized, double blind, placebo-controlled trial. Ann Intern Med 1995; 123: 241-9.

13 McGoldrick D, George RB. Nonnarcotic analgesics: Prevalence and estimated economic impact of toxicities. Ann Pharmacother 1997; 31: 221-7.

14 John P, David H. Consumption of NSAIDs and the development of congestive heart failure in elderly patients. Arch Intern Med 2000; 160: 777-83.

15 McCarthy DM. Comparative toxicity of nonsteroidal anti-inflammatory drugs. Am J Med 1999; 107: 37-46.

16 Davd H, Lynette LY, Luis AG. Variability in risks of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: result of a collaborative meta-analysis. Br Med J 1996; 312: 1563-6.

17 Anne VH, Jules IS, Marleen D. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on cox-2 verse cox-1 in health volunteers. J Clin Pharmacol 2000; 40: 1109-20.

18 McQueen S, Hutton D, Allen A. Gastric and duodenal surface mucus gel thickness in rat: effects of prostaglandins and damaging agents. Am J Physiol 1983; 245: 388.

19 Fries JF. How many quality of life for rheumatoid arthritis patients be enhanced by current and future treatment. Rheumatology (Oxford) 1999; 38: 35-40.

20 Li L, Wang HM, Shen Y. Chinese SF-36 health survey: translation, cultural adaptation, validation, and normalization. J Epidemiol Community Health 2003; 57: 259-63.

21 Hill CL, Parson J, Taylor A. Health related quality of life in a population with arthritis. J Rheumatol 1999; 26: 2029-35.