Blood Pressure Destabilization and Edema Among 8538 Users of Celecoxib, Rofecoxib, and Nonselective Nonsteroidal Antiinflammatory Drugs (NSAID) and Nonusers of NSAID Receiving Ordinary Clinical Care

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ABSTRACT. ***Objective.*** To investigate the relationship between nonselective nonsteroidal antiinflammatory drugs (NS NSAID), rofecoxib, celecoxib, and risk of edema and blood pressure destabilization in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) receiving ordinary clinic care.

Methods. Patients participating in a longterm outcome study reported drug use, as well as the presence of edema and blood pressure increases occurring during the previous 6 months. To measure pure drug effect, analyses were restricted to 8538 patients who exclusively used a NS NSAID, rofecoxib, or celecoxib, and compared to nonusers of NS NSAID, rofecoxib, or celecoxib. We evaluated blood pressure destabilization using patient-reported increases in blood pressure and/or difficulty in controlling blood pressure.

Results. Compared with nonusers, after adjusting for age, sex, presence of RA, and history of heart disease and hypertension, patients using rofecoxib, but not celecoxib or NS NSAID, had an increased rate of edema (23.3% vs 18.0%), while the rates for celecoxib and NS NSAID were 17.5% and 18.2%, respectively. The adjusted risk of edema was significantly increased for rofecoxib compared to celecoxib (OR 1.33, 95% CI 1.08–1.64). For blood pressure increases, among patients who did not report having hypertension, no significant increase was noted for NS NSAID and celecoxib compared with nonusers. However a significant increased risk of blood pressure increase was seen for rofecoxib (OR 2.08, 95% CI 1.41–3.06). Among patients who reported having hypertension, patients taking rofecoxib had a significant increased risk of blood pressure increase compared to nonusers (OR 1.55, 95% CI 1.23–1.96), while the risks of blood pressure increase for users of celecoxib and NS NSAID were not significantly different than among nonusers. After controlling for age, sex, RA, and new starts on NSAID, the risk of blood pressure increase was significantly higher for users of rofecoxib than celecoxib (OR 1.21, 95% CI 1.03–1.61) among patients with hypertension, and numerically higher for nonhypertensives (OR 1.42, 95% CI 0.96–2.22). The increased risk for hypertension and edema of rofecoxib compared to celecoxib users was further confirmed by analysis of specific reported side effects during 2 separate 6-month periods (July 1 to December 31, 1999, and January 1 to June 30, 2000). During these 2 periods, rofecoxib-treated patients were 2.16 to 3.82 times more likely to report edema or blood pressure increase side effects compared to celecoxib-treated patients.

Conclusion. Rofecoxib, but not celecoxib and NS NSAID, is associated with an increased risk of edema and blood pressure increase compared to nonusers of NSAID. (J Rheumatol 2004;31:1143–51)

Key Indexing Terms:
NONSTEROIDAL ANTIINFLAMMATORY DRUG CYCLOOXYGENASE-2
ADVERSE EVENTS HYPERTENSION EDEMA

Hypertension and arthritis are among the most common chronic conditions in the United States today. Data from the Third National Health and Nutrition Survey (NHANES) placed the prevalence of hypertension at approximately 32%[1]. Based on 2001 data from the National Data Bank for Rheumatic Diseases (NDB), 30.1% of 14,077 patients with rheumatoid arthritis (RA) and 40.2% of 3459 with osteoarthritis (OA) currently have hypertension[2]. Blood pressure control has clearly been shown to reduce the risk of coronary heart disease, heart failure, and stroke[3-6]. Improving the percentage of hypertensive patients controlling their blood pressure is a major

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public health challenge (National Institutes of Health), as is preventing its elevation.

Many factors, however, interfere with blood pressure control: one is nonsteroidal antiinflammatory drug (NSAID) utilization. Two metaanalyses examined the effect of NSAID on blood pressure. While the metaanalyses did report that NSAID increased blood pressure, the effect was most pronounced in patients with hypertension or in treated hypertensive patients, and lowest in normotensive patients not taking blood pressure medications. Further, there was a considerable variability between NSAID in their effect on blood pressure. Indomethacin, naproxen, ibuprofen, and piroxicam treatment had the greatest effect on blood pressure, while aspirin and sulindac had the least effect[7,8].

Cyclooxygenase-2 (COX-2) specific inhibitors also have an effect on blood pressure destabilization and edema[9-11]. For example, a post-hoc analysis of the celecoxib clinical development program database, including more than 13,000 subjects in 50 clinical studies, reported that the incidence of renal adverse events for celecoxib was greater than placebo, but similar to nonspecific NSAID (NS NSAID)[12].

Most recently, attention has shifted to examining the effects of the COX-2 specific inhibitors celecoxib and rofecoxib on blood pressure control and peripheral edema. Two recent head-to-head trials reported differences within the COX-2 specific inhibitor class, with significantly lower incidences of destabilized blood pressure and edema with celecoxib 200 mg QD compared with rofecoxib 25 mg QD in persons aged 65 and older with OA and hypertension[13,14]. In addition, results from a World Health Organization (WHO) spontaneous adverse drug reaction monitoring center also suggested more renal, edema, and hypertension problems with rofecoxib compared to celecoxib[11]. However, dose issues make the interpretation of results difficult, as celecoxib is often used in higher daily doses ($\geq$ 400 mg/day) and rofecoxib at the lower dose ($\leq$ 25 mg/day).

While trials are useful for examining treatment effects in the randomized controlled trial (RCT) setting, use in routine clinical practice may deviate from use in RCT, and so may results. We evaluated the incidence of self-reported blood pressure destabilization and edema in a large population of rheumatic disease patients participating in the National Data Bank for Rheumatic Diseases. We designed a special questionnaire to examine rates and changes in edema and hypertension in this group, particularly in regard to NSAID usage and hypertension status.

MATERIALS AND METHODS

As part of an ongoing evaluation of rheumatic diseases, 9226 patients, of whom 76.8% had RA and 23.2% had OA of the knee or hip, completed a detailed mailed survey in January 2001 concerning their illness and treatment in the preceding 6 months. Patients in this study are participants in the NDB outcomes research study, and were enrolled from the practices of 591 US rheumatologists who also provided diagnostic information[15]. The NDB population is typical of RA survey populations, but is slightly overrepresented by nonminorities and those with greater education. The purpose of the study was to investigate the properties of the COX-2 specific inhibitors celecoxib and rofecoxib, compared to patients who received nonselective (NS) NSAID and to nonusers of NS NSAID. Six hundred eighty-eight (n = 688) patients who were in more than one of the 3 treatment groups were excluded from analysis. Of the 8538 patients remaining, 2863 received no NSAID, 3159 received a NS NSAID, 991 received rofecoxib, and 1525 received celecoxib. RA was diagnosed in 77.9% and knee or hip OA in 22.1% of patients in the 8538-patient study data set.

Demographic and clinical data. At each questionnaire assessment, demographic variables were recorded, including sex, age, ethnic origin, education level, and current marital status. Study variables included the Stanford Health Assessment Questionnaire (HAQ) functional disability index (HAQ disability)[16,17], a visual analog scale (VAS) for pain, a VAS global disease severity, VAS sleep and fatigue scales[18], the Arthritis Impact Measurement Scales (AIMS)[19,20], anxiety and depression scales[21,22], the Medical Outcome Study Short Form-36 (SF-36) mental and physical component scales (MCS and PCS)[23], the Western Ontario and McMaster University (WOMAC) pain, stiffness and function scale[24,25], and Likert scales that assessed current satisfaction with health and current perceived health. To measure "Health quality of life" we used the VAS from the EuroQol[26,27]. To assess gastrointestinal (GI) symptom severity we used a VAS that read, "How much trouble have you had with your stomach (i.e., nausea, heartburn, bloating, pain, etc.)? Place a mark on the line that best describes the severity of your stomach problems on the scale of 0–100."

Specific study questions. To evaluate edema during the previous 6 months, the following question was used: "Did you notice any swelling (edema) of your body parts that were not due to arthritis?" To investigate blood pressure issues during the previous 6 months, the following questions were used: "Did you become aware of any increase in your blood pressure?" and "Did you have any problem controlling your high blood pressure?" Yes/no check boxes were provided after each question.

In addition, all participants report medication used and patient's attribution of adverse effects of medication. We studied attributions of edema and hypertension for the study drugs.

Validation data for hypertension. To validate patient's reports of hypertension, we examined hypertensive medications patients were taking and compared the usage of such medications to the report of hypertension. A high level of concordance was found, in that 90.6% of patients reporting hypertension were using antihypertensive medications. In addition, among patients reporting difficulty in controlling blood pressure, 75.3% indicated that their antihypertensive medications were increased in dose, were changed to another antihypertensive medication, or that they had an additional antihypertensive medication added.

For a confirmatory analysis of edema and hypertension reported as side effects by patients, we also examined questionnaire reports for 2 different periods: July 1, 1999, through December 31, 1999, and January 1, 2000, through June 30, 2000. Of 146 patients reporting side effects related to edema or hypertension, 8.9% of patients reported a side effect in both periods.

Statistical methods and interpretation. The primary method of analysis used in this study was multivariate logistic regression, with adjustments for age, sex, RA versus non-RA, new starts on COX-2 drugs versus continuation on COX-2 drugs, hypertension and cardiovascular disease, as indicated and as described in the text. In these analyses the primary comparison was the 3 individual drug treatment groups with the no-treatment group. Specifically, the odds ratios for the drug groups are the odds ratio for each group compared with the no-treatment group. For clarity, where required, paired-group comparisons were made using the Wald test, which tests the hypothesis that the coefficients of the groups being compared are equal. Adjusted prevalence values used mean covariate levels of the combined study cohort. The Stata statistical package version 7.0 was used[28]. Statistical significance was set at 0.05 and all tests were 2-tailed.

RESULTS

Group differences in demographic and severity characteristics. Table 1 presents the demographic, comorbidity, and disease severity characteristics of the 4 study groups. Based on previous research, we expected the two COX-2 groups to report more abnormal severity scores and more comorbid condition because of channeling bias and confounding by indication[29]. As shown in Table 1, the most abnormal scores for pain, global severity, helplessness, HAQ, WOMAC, and SF-36 scores, among others, were found in the COX-2 groups. Because of the large sample sizes, the differences, often small, were always statistically significant (statistical analyses not shown). The COX-2 specific inhibitor groups also had reported greater lifetime history of GI ulcer disease, as would be expected by the operating prescription bias. One other difference of note was that only 68.9% of rofecoxib patients had RA compared to 78.1% of celecoxib patients. This difference was also to be expected, as rofecoxib was not approved for use in RA at the time of this study. In spite of the differences between COX-2 and the other groups, the two COX-2 groups were quite similar for the study variables of Table 1.

Edema

Group differences in the rate of edema. We observed 19.4%, 18.4%, 19.1%, and 25.8% of patients on no NSAID, NS NSAID, celecoxib, and rofecoxib, respectively, reported the presence of edema. Because these crude values do not account for the covariate status, a series of regressions were performed to better define rates and associations of edema (Tables 2 and 3). Table 2 presents the edema data adjusted for age, sex, and RA. This analysis shows that there is no significant difference between the nonuser group, the NS NSAID group, and the celecoxib group. However, rofecoxib users were 1.37 times more likely to report edema than nonusers (OR 1.37, 95% CI 1.15–1.63, $p < 0.001$). In addition, the OR differed significantly between the rofecoxib and celecoxib groups by the Wald test, indicating a greater risk of edema among rofecoxib compared to celecoxib

Table 1. Demographic and clinic data for 8538 study participants.

Variable	Non users, n = 2,863		NS NSAID, n = 3, 159		Rofecoxib, n = 991		Celecoxib, n = 1525	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Demographics								
Age, yrs	64.27	12.70	59.45	12.50	62.16	12.33	62.48	12.05
Education, yrs	13.32	2.31	13.69	2.30	13.63	2.25	13.59	2.24
Sex, % male	22.70		21.35		18.48		21.59	
White (non-Hispanic), %	92.10		92.70		94.03		93.63	
RA, % positive	78.45		80.06		68.90		78.09	
Severity measures								
Global severity (0–10)	3.23	2.52	3.08	2.41	3.57	2.51	3.39	2.43
Health status (0–3)	1.45	0.75	1.37	0.73	1.50	0.72	1.46	0.73
Health satisfaction (–2 to 2)	–0.37	1.22	–0.41	1.20	–0.14	1.25	–0.29	1.19
Helplessness (5–25)	11.14	5.00	10.87	4.76	11.90	5.09	11.33	4.83
Pain (0–10)	3.50	2.81	3.50	2.62	3.98	2.75	3.82	2.68
Anxiety (0–10)	3.35	1.95	3.27	1.83	3.56	1.96	3.39	1.85
HAQ disability (0–3)	1.07	0.76	1.00	0.70	1.10	0.71	1.09	0.69
Depression (0–10)	2.34	1.73	2.19	1.57	2.44	1.76	2.33	1.63
Fatigue (0–10)	4.09	2.95	3.96	2.82	4.36	2.89	4.31	2.88
GI symptom severity (0–10)	1.79	2.38	1.69	2.23	2.14	2.54	1.98	2.42
Sleep disturbance (0–10)	3.36	3.05	3.19	2.93	3.82	3.08	3.54	2.95
Quality of life (0–100)	68.40	21.54	70.17	20.68	66.76	21.36	68.57	20.21
WOMAC pain (0–50)	13.76	12.17	13.57	11.49	16.24	12.19	15.03	11.73
WOMAC stiffness (0–20)	6.37	5.35	6.43	5.12	7.37	5.36	6.95	5.19
WOMAC function (0–170)	47.08	41.76	44.01	39.12	51.31	41.43	49.72	39.99
SF-36 physical scale	33.02	8.62	33.72	8.25	32.08	8.24	32.26	8.05
SF-36 mental scale	44.89	14.05	45.95	13.14	43.18	14.08	44.19	13.59
Comorbidity								
Lifetime comorbidity count (0–9)	1.62	1.52	1.36	1.38	1.77	1.47	1.66	1.42
Myocardial infarction, % ever	6.13		3.96		4.74		6.10	
Other CV diseases, % positive	9.39		6.08		9.08		9.11	
Total CV disease, % positive	14.4		9.34		12.41		13.44	
CVA, % positive	3.48		2.28		2.62		3.28	
Hypertension, % ever	44.16		39.27		46.52		46.62	
GI ulcers, % ever	13.27		8.96		15.04		15.74	

HAQ: Health Assessment Questionnaire, GI: gastrointestinal, WOMAC: Western Ontario and McMaster University OA Index, CVA: cardiovascular accident.

Table 2. Rates and odds ratios for edema according to treatment group (all patients).

	N	OR	p	Lower 95% CI	Upper 95% CI	Adjusted* Rate, %
Nonusers (comparison group)	2785	1.00				19.0
NS NSAID	3090	0.96	0.599	0.84	1.10	18.5
Celecoxib	1464	0.98	0.817	0.83	1.15	18.7
Rofecoxib	954	1.37	0.000	1.15	1.63	24.3
Rofecoxib = celecoxib†			0.001			

* Adjusted for age, sex, and presence of RA. † A significant p value indicates that the OR for rofecoxib and celecoxib are significantly different. 2.9% of subjects did not complete this question.

Table 3. Rates and odds ratios for edema according to treatment group. COX-2 users are restricted to those who began the COX-2 drug during the 6-month observation period.

	N	OR	p	Lower 95% CI	Upper 95% CI	Adjusted Rate, %
Nonusers (comparison group)	2785	1.00				18.8
NS NSAID (includes new and continuing users)	3090	0.98	0.716	0.85	1.12	18.4
Celecoxib	217	1.08	0.682	0.76	1.52	19.9
Rofecoxib	201	1.62	0.003	1.18	2.24	27.23
Rofecoxib = celecoxib†			0.075			

* Adjusted for age, sex, and presence of RA. † A significant p value indicates that the OR for rofecoxib and celecoxib are significantly different. 2.6% of subjects did not complete this question.

users. The OR for the risk of edema was 1.39 (95% CI 1.14–1.70, p = 0.001) for rofecoxib compared to celecoxib.

New starts on COX-2 therapy versus those continuing COX-2 specific inhibitor therapy: edema. To further elucidate these changes, we subdivided the COX-2 specific inhibitor groups into those who started their COX-2 specific inhibitor during the previous 6 months and those who had been receiving the drug prior to that period. New starts occurred in 27.2% of rofecoxib users and 19.9% of celecoxib users. Table 3 indicates that among those COX-2 patients who began their drug within the last 6 months, new rofecoxib users were 1.62 times more likely to report edema than nonusers (OR 1.62, 95% CI 1.81–2.24, p = 0.003). The risk of edema was not significantly increased for celecoxib (OR 1.08, 95% CI 0.76–1.52, p = 0.680).

The increased risk of edema among rofecoxib users and higher rates of edema among new starts led us to further characterize the effect of new versus old COX-2 specific inhibitor usage by restricting analysis of Table 2 and adding a dummy variable for new COX-2 specific inhibitor usage. This analysis indicated a nonsignificant effect for the new-start variable (OR 1.17, 95% CI 0.91, 1.50), but an increased risk of swelling for rofecoxib compared to celecoxib (OR 1.37, 95% CI 1.13–1.67, p < 0.001) still remained.

Effect of hypertension and heart disease on the risk of edema. As indicated in Table 1, a history of cardiovascular disease and hypertension are more common among those using COX-2 specific inhibitors compared to those using NS NSAID. To understand whether this comorbidity influenced edema, and whether this, in turn, influenced the effect of drug group on edema, we added 2 dummy variables for cardiovascular disease and hypertension to the analysis of the regression shown in Table 2. Table 4 indicates that persons reporting cardiovascular comorbidity also reported more edema (OR 2.07) and that those reporting hypertension similarly reported more edema (OR 1.83). These dummy variables added additional control to the analyses of the effect of drug group. In these analyses, rofecoxib still is associated with increased risk of edema (OR 1.39). The rofecoxib rate of edema is 23.3% compared with 17.5% for celecoxib (p < 0.001). It is also of interest that patients with RA were less likely to report edema (OR 0.64), as were men (OR 0.60). The reason for this is not clear, but it is possible that some patients with RA attributed edema to synovitis.

Confirmation analysis based on the edema events reported as a side effect of treatment. For validation, we also compared the rate of edema reported as a side effect between treatment of celecoxib and rofecoxib. For the period July 1, 1999, and December 31, 1999, the incidence rate ratio (IRR) for rofecoxib compared to celecoxib for reported edema side effect was 2.29 (95% CI 1.28–4.12). The IRR for the period January 1, 2000, and June 30, 2000, was 3.82 (95% CI 2.34–6.41).

Summary: Edema and NSAID drug use. The results indicate

Table 4. The effect of NSAID therapy on the presence of edema controlling for age, sex, RA, lifetime history of cardiovascular disease, and hypertension.

Category	N	OR	p	Lower 95% CI	Upper 95% CI	Adjusted Rate, %
Nonusers (comparison group)	2785	1.00				18.0
NS NSAID	3090	1.02	0.808	0.89	1.17	18.2
Celecoxib	1464	0.97	0.696	0.82	1.14	17.5
Rofecoxib	954	1.39	0.000	1.16	1.66	23.3
Age, yrs		1.00	0.723	0.99	1.00	
Sex (male = 1, female = 0)		0.60	0.000	0.52	0.70	
RA (0/1)		0.64	0.000	0.56	0.73	
Heart disease ever (0/1)		2.07	0.000	1.78	2.41	
Hypertension (0/1)		1.83	0.000	1.63	2.05	
Rofecoxib = celecoxib†			0.000			

* Adjusted for age, sex, and presence of RA, history of heart disease and hypertension. † A significant p value indicates that the OR for rofecoxib and celecoxib are significantly different. 2.9% of subjects did not complete this question.

that users of NS NSAID and celecoxib do not differ from nonusers of NSAID in the reporting of edema. However, rofecoxib users have increased rates of edema compared to all groups including the celecoxib group.

Hypertension

The relationship between NSAID status and hypertension was evaluated by assessing increases in blood pressure and/or difficulty in controlling blood pressure. The unadjusted rates for blood pressure increase were 15.2% for nonusers, 16.1% for NS NSAID, 18.7% for celecoxib, and 23.2% for rofecoxib users. Since hypertension was significantly associated with the 2 blood pressure destabilization measures, we conducted analyses by stratifying patients into 2 groups based on patients reporting having or not having hypertension. These analyses were also controlled for age, sex, presence of RA condition, and history of heart diseases. Table 5 shows that among patients in either the hypertensive or normotensive group, rofecoxib was significantly associated with a blood pressure increase. Compared to nonusers, the OR for rofecoxib was 1.55 (95% CI.1.23–1.96) among patients with hypertension. The OR for rofecoxib was 2.08 (95% CI 1.41–3.06) among patients without a hypertensive condition. In comparison with the nonuser group, no significant differences were found ($p > 0.05$, see Table 5 for values) for blood pressure increase among users of NS NSAID and celecoxib in either hypertensive or normotensive patients. Rofecoxib was more likely to be associated with blood pressure increase than celecoxib among patients having hypertension (OR 1.21, $p < 0.05$). The difference in blood pressure increase between rofecoxib and celecoxib among patients without hypertension was not statistically significant (OR 1.42, $p = 0.07$), but the overall trend of rofecoxib being associated more with increased blood pressure was clear across the groups. Table 5 also showed that increases in blood pressure occurred primarily in patients with a history of hypertension. The incidence rate for blood pressure increase was 39.1% among rofecoxib users, 32.4%

Table 5. The association of NSAID therapy with blood pressure increase.

	N	OR	p	Lower 95% CI	Upper 95% CI	Adjusted Rate, %
Hypertensive patients						
Nonusers (comparison group)	1167	1.00				29.3
NS NSAID	1204	1.12	0.223	0.93	1.34	31.7
Celecoxib	679	1.16	0.166	0.94	1.42	32.4
Rofecoxib	437	1.55	0.000	1.23	1.96	39.1
Rofecoxib = celecoxib†			0.024			
Normotensive patients						
Nonusers (comparison group)	1498	1.00				4.50
NS NSAID	1882	1.12	0.488	0.81	1.54	5.02
Celecoxib	774	1.42	0.069	0.97	2.07	6.3
Rofecoxib	512	2.08	0.000	1.41	3.06	8.92
Rofecoxib = celecoxib†			0.074			

* Adjusted for age, sex, and presence of RA and history of heart disease.. † A significant p value indicates that the OR for rofecoxib and celecoxib are significantly different. 3.3% of subjects did not complete this question.

among celecoxib users, 31.7% for NS NSAID, and 29.3% for nonusers. However, among patients who did not report having hypertension, the incidence rate of blood pressure increase was nearly one-sixth (5.5% vs 32.0%) of that among patients with hypertension.

The comparison of "difficulty to control blood pressure" was conducted among patients with hypertension, as that measure is irrelevant to patients who did not report having hypertension. Table 6 showed that rofecoxib was significantly associated with difficulty controlling blood pressure among patients with hypertension (OR 1.38 vs no-NSAID group). Patients using celecoxib (OR 1.18) and NS NSAID (OR 1.08) had similar rates for patients reporting difficulty controlling blood pressure compared to patients in the nonuser group (OR 1.0, $p > 0.05$; see Table 6 for values).

Confirmation analysis based on the hypertension events reported as a side effect of treatment. For validation, we also studied the rate of hypertension reported as a side effect of treatment for celecoxib and rofecoxib. For the period July 1, 1999, and December 31, 1999, the IRR for rofecoxib compared to celecoxib for reported hypertension as a side effect was 2.16 (95% CI 0.83–5.66). The IRR for the period January 1, 2000, and June 30, 2000, was 3.06 (95% CI 1.30–7.72).

Consequences of edema and increase in blood pressure. Because congestive heart failure (CHF) might be related to edema or blood pressure increase, we evaluated the effect of edema and CHF on these outcomes. Patients reporting edema had a 4-times increased risk of CHF (OR 4.02 3.12–5.17), and those reporting blood pressure increase had an OR for CHF of 1.69 (1.33–2.14). The overall risk of CHF was low in this cohort (3.2%), and we found no significant association between drug therapy (including specific NSAID groupings) and CHF, regardless of edema status. We also examined the risk of treatment termination. The risk of treatment termination was low (6.9%) because of the study requirement that patients be taking only one NSAID during the 6-month study period. Patients reporting edema were more likely to terminate therapy (OR 1.48; 1.17–1.86), as were patients reporting blood pressure increase (OR 1.60; 1.19–2.15). However, as with CHF, we found no significant interaction between treatment(s) and blood pressure increase and the risk of treatment termination.

Crude rates for specific NSAID. The rates of edema and increases in blood pressure associated with specific NSAID are shown in Table 7.

DISCUSSION

The impetus for this study was the observation coming from clinical trials and spontaneous reporting data bases that rofecoxib was associated with increased edema and hypertension compared to celecoxib[11,13]. This observation took on more importance with the publication of the VIGOR trial, in which patients receiving the COX-2 specific NSAID rofecoxib had an increase in myocardial infarction compared to patients who received naproxen, a nonspecific NSAID[30]. In addition, product labeling indicates an increase in edema for rofecoxib. On the other hand, both rofecoxib and celecoxib are similar drugs in regard to their COX effects, and it might be expected that the pattern of adverse effects would be similar. Nor are NS NSAID harmless in regard to adverse effects such as hypertension, with a number of studies implicating this class of drug in the genesis of hypertension-related adverse effects[31,32].

With this as a background, we designed a study specifically to test the relationships of the various drugs and drug classes in regard to these 2 common adverse events. Unlike the WHO database of spontaneously reported adverse events[11], we surveyed a large cohort of patients prospectively and examined reported events, whether they were classified as side effects or not. We did this by including direct questions about these events. We did not ask about these events as side effects so as not to bias the reporting. In determining edema, we asked patients to report swelling in their body that was not caused by arthritis. This type of question differs from the usual physician-determined adverse event in that it is not subject to validation by physician, and what the patient means by edema may be different from the definition used in clinical trials. In addition, our inquiry addressed all edema, not simply new swelling. As expected, the rates reported here are higher than those from clinical trials. Therefore, although the absolute rate as perceived by patients is of interest, the differences between drugs and drug classes is of special importance.

The results of this study confirm the finding of the clin-

Table 6. The association of NSAID therapy with difficulty in controlling blood pressure.

	N	OR	p	Lower 95% CI	Upper 95% CI	Adjusted Rate, %
Hypertensive patients						
Nonusers (comparison group)	1147	1.00				16.5
NS NSAID	1164	1.08	0.495	0.87	1.33	19.8
Celecoxib	654	1.18	0.186	0.92	1.50	21.2
Rofecoxib	417	1.38	0.021	1.05	1.81	24.0
Rofecoxib = celecoxib[†]			0.289			

* Adjusted for age, sex, and presence of RA and history of heart disease.. [†] A significant p value indicates that the OR for rofecoxib and celecoxib are significantly different. 7.3% of subjects did not complete this question.

Table 7. Crude rates of edema and hypertension by specific NSAID.

NSAID	N Edema (BP+, BP–)	Edema, %	95% CI	BP Increase, Hypertension (+), %	95% CI	BP Increase, Hypertension (–), %	95% CI
Celecoxib	1464	19.1	16.9–21.4	32.7	28.5–37.3	6.5	4.8–8.5
Rofecoxib	954	25.8	22.7–29.2	39.6	33.9–45.9	9.2	6.7–12.2
Ibuprofen	691	16.1	13.2–19.3	37.5	30.2–46.1	4.9	3.1–7.4
Naproxen	630	16.8	13.8–20.3	33.5	26.5–41.7	3.8	2.1–6.2
Nabumetone	345	21.2	16.6–26.6	30.6	22.3–41.0	5.7	2.8–10.2
Diclofenac	230	15.7	11.0–21.7	31.1	21.3–43.9	4.9	1.8–10.6
Sulindac	168	20.2	14.0–28.3	43.4	29.9–61.0	4.3	1.2–11.0
Etodolac	158	16.5	10.8–24.1	28.3	15.8–46.7	5.1	1.6–11.8
Salsalate	148	18.9	12.6–27.3	28.8	17.3–45.0	2.3	0.3–8.2
Oxaprozin	134	22.4	15.1–32.0	31.1	17.0–52.2	9.2	4.0–18.1
"Arthrotec"	127	22.8	15.3–32.8	45.8	30.2–66.6	4.3	0.9–12.5
Piroxicam	99	15.2	8.5–25.0	35.1	18.7–60.1	6.3	1.7–16.3
Ketoprofen	91	14.3	7.6–24.4	28.6	13.7–52.5	7.0	1.9–18.0
Indomethacin	54	20.4	10.2–36.4	20.0	5.5–51.2	6.1	0.7–21.9
Meloxicam	51	27.5	15.0–46.1	44.8	23.9–76.7	17.4	4.7–44.5
Flurbiprofen	32	9.4	1.9–27.4	14.3	1.7–51.6	5.9	0.1–32.8
Tolmetin	25	12.0	2.5–35.1	27.3	5.6–79.7	0.0	0.0–28.4
Meclofenamate	9	0.0	0.0–41.0	0.0	0.0–368.8	0.0	0.0–41.0
Fenoprofen	6	50.0	10.3–146.1	0.0	0.0–368.8	0.0	0.0–73.8

Rates are crude (unadjusted) and expressed per 100 patients exposures (%). BP + and hypertension (+): increase in blood pressure in patients with history of hypertension. BP – and hypertension (–): increase in blood pressure in patients without a history of hypertension.

ical trials that use of rofecoxib is associated with increased edema compared to use of NS NSAID and celecoxib and non-use. Of interest, the data of this study rely on dosages that are common in practice: only 9% of those receiving rofecoxib used the 50 mg dose of rofecoxib per day (high dose) compared with 52% of celecoxib users who used the higher (400 mg) dose of celecoxib daily. For rofecoxib and celecoxib, respectively, the mean, median, and doses ranges were 26, 25, 13–100 mg and 299, 250, 100–1600 mg.

The case of hypertension is more complicated. Our question, "Did you have an increase in your blood pressure," was designed to record new cases of hypertension as well as loss of control of treated hypertension. Hypertension questions are difficult, as patients with hypertension may not report hypertension if it is controlled. Therefore we addressed this question by using the term increase in "blood pressure" rather than "hypertension" in describing this outcome. It should also be noted that if a patient did not have his blood pressure measured during the study assessment period then it is possible that blood pressure increase might have gone undetected. As with edema, then, the increase in blood pressure measure of this study has particular value as a comparative measure in addition to the value it has as an absolute measure.

In addition, because the incidence rate of blood pressure increase may differ between patients with or without hypertension, we analyzed the blood pressure increase measure by stratifying patients who reported having or not having hypertension. The results of this analysis suggest that blood pressure increase occurs with rofecoxib in both hypertensive and nonhypertensive groups. In this analysis, the incidence rate of blood pressure increase for patients who reported having hypertension was 5.8 times (32.0% vs 5.5%) greater than those not having such condition.

One limitation of this study is the concern that information about the putative increase in rofecoxib-related hypertension and edema that was brought to physicians by marketing representatives might have influenced physicians and patients to be hypervigilant in identifying these events. If that were the case, at least part of the effect that we observed in this report could be attributed to this external bias. To investigate this possibility, we examined the rate of edema and hypertension as a reported side effect during the periods January 1, 2000–June 30, 2000 and July 1, 1999–December 31, 1999, the times before marketing representatives could have influenced physicians. The analyses indicated that the incidence rate ratios (IRR) for reported edema and hypertension side events among rofecoxib users were significantly higher than those among celecoxib users during this time period. This consistency of effect prior to the marketing campaign provides strong evidence for the validity of the current data. Another possible limitation is that patients usually only know about increases in blood pressure when this is communicated to them by medical staff. Therefore, it is possible that physician bias could have inflated the reporting in some cases and decreased it in others.

Another potential limitation of the study is that we may have underestimated the adverse effects by our conservative methodology of excluding patients who received more than

one drug or drug class. In part, this was done because our methodology does not allow us to attribute effects when more than one NSAID was used. For example, using the strict entry criteria of this study, the IRR for rofecoxib compared to celecoxib for hypertension was 1.98 (95% CI 0.65–6.25). However, when all patients are studied the IRR for hypertension is 3.52 (95% CI 1.64–8.22). This suggests that elimination of patients who were taking more than one drug during the 6 month period might have led to apparent reduced rates of edema or hypertension increase.

Still another limitation is that the study deals with prevalent data and cannot address the issue of incidence of hypertension and edema change.

Among the clinical consequences of edema and increased blood pressure are alteration or discontinuation of antihypertensives and diuretics, with consequent burden on the patient and increased costs. Termination of NSAID therapy may also be a consequence. This study also confirmed the well known finding that persons with edema and increased hypertension are more likely to report CHF and to discontinue NSAID treatment. It is important to note that the relatively high rates of edema and increase in hypertension occurred across all treatment groups, including those not using NSAID. While we found that rofecoxib had higher rates of edema and blood pressure increase compared with celecoxib, the actual difference in rates was small, about 5–6%. We did not find increased rates of CHF associated with specific treatments, but our period of followup may have been too short to detect a specific drug effect if one actually exists. In addition, the method of the study, selecting patients taking only one drug during the 6-month study period, works against finding such an effect. Clinically, our data suggest vigilance in monitoring edema and blood pressure in patients with RA and OA, with perhaps some extra vigilance for those receiving rofecoxib, given these results.

In summary, based on patients' self-reported data, rofecoxib but not celecoxib is associated with increased risk of edema and blood pressure increase compared to nonusers of NSAID. The risks of edema and blood pressure increase among users of rofecoxib were significantly higher than in those using celecoxib. The differences in these risks between celecoxib and NS NSAID were not significant. As all patients receiving NSAID therapy may be at risk for edema and hypertension, it is important that they be evaluated for this possibility during the time of NSAID therapy.

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