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Use of Nonsteroidal Anti-inflammatory Drugs and Risk of Fractures

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In animal models, prostaglandin synthesis has been found to mediate bone metabolism. Nonsteroidal anti-inflammatory drugs (NSAIDs), given their inhibitory effects of prostaglandin synthesis, may play a role in the prevention of osteoporosis. The primary objective of this study is to describe and quantify the fracture risks of patients exposed to NSAIDs in a representative general medical practice setting. A retrospective cohort study was conducted in a general medical practice setting in the UK (using data from the General Practice Research Database). Regular NSAID users (who received three or more NSAID prescriptions), aged 18 years or older, were compared with matched control patients and incidental NSAID users. The study comprised 214,577 regular NSAID users, 286,850 incidental NSAID users, and 214,577 control patients. The relative rate of nonvertebral fractures during regular NSAID treatment compared with control was 1.47 (95% confidence interval [CI] 1.42–1.52) and that of hip fracture 1.08 (0.98–1.19). No differences in nonvertebral fractures were found between the regular and incidental NSAID users (RR = 1.04; 95% CI 0.99–1.09). The rate of nonvertebral fractures among users of diclofenac (RR = 1.00; 95% CI 0.93–1.08) and naproxen (RR = 0.91; 95% CI 0.82–1.00) was similar to that of ibuprofen. The results of this study are not supportive of clinically significant effects of NSAIDs on bone metabolism. (Bone 27:563–568; 2000)

Key Words: Prostaglandin; Osteoporosis; NSAIDs.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins, which are known to stimulate the resorption of bone by osteoclasts. There is evidence from animal studies that NSAIDs may slow bone loss.[8,16,19,29,36,37] Two studies in humans reported significantly higher bone density among NSAID users compared with nonusers.[3,24] One study of 932 women observed a 9% higher lumbar spine density among users of propionic acid NSAIDs.[24] The other study reported that daily use of aspirin or NSAIDs in 7786 elderly women was associated with a 2.3%–5.8% increase in bone density of the hip and spine. This increase in bone density was not however associated with a reduction in risk of fracture (relative rate of nonvertebral fracture of 1.0).[3] Reductions in fractures among NSAID users were, however, seen in two other studies. A significant reduction of 68% in the risk of hip fracture with NSAID use was found in a study of 280 elderly women.[28] Rashiq and Logan[26] also observed a reduction of hip fracture risk (by 46%), but this difference was not statistically significant. The relationship between duration of NSAID use, type of NSAID, and fracture risk is unknown. Given these conflicting results, further analysis of fracture risk in a large cohort of NSAID users is requisite. The primary objective of this study is to describe and quantify the fracture risks of patients given NSAIDs in a representative general medical practice setting.

Materials and Methods

The information in this study was obtained from the General Practice Research Database (GPRD), which comprises the computerized medical records of general practitioners. General practitioners (GPs) play a key role in the UK health-care system as they are responsible for primary health care and specialist referrals. Patients are semipermanently affiliated with a practice that centralizes the medical information not only from the GPs themselves but also from specialist referrals and hospitalizations. The current study included 683 practices from different geographic areas in the United Kingdom. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, and hospital admissions and their major outcomes.[2,11,12,20,22,35] Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OXMIS) codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9).[2,20] Each entry into the GPRD is internally validated by cross-checking within the practice and by comparisons with external statistics.[2,11,12,20,22,35] Only data from practices that pass this quality control are compiled into the GPRD database. Several independent validation studies have confirmed a high level of completeness and validity of the GPRD.[14,15,25,31] The GPRD is owned by the Medicines Control Agency, UK.

Study Population

A nonconcurrent (retrospective) cohort study was conducted comparing patients using NSAIDs with control patients. The study was conducted in a cohort of people who received nonsystemic corticosteroids (topical, aural, ophthalmic, or nasal). This was done for practical reasons as the data were available

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from a previous study.[32] Within this cohort, the NSAID takers were defined as permanently registered patients aged 18 years or older who received one or more prescriptions for NSAIDs during the period of time from the enrollment date of their practice in GPRD up to the end of data collection (December 1997). The group of NSAID users was divided into patients who received three or more NSAID prescriptions and patients who received one or two prescriptions. The NSAID prescriptions were prescribed between 1987 and 1997, with the median prescription written in 1992. One control group was randomly selected out of the cohort of nonsystemic corticosteroids users, consisting of patients who never received systemic NSAIDs.[5] The control patients were matched by age (within 5 years and, if no patient found, within 10 years), gender, and, if possible, medical practice. Topical corticosteroids were the most frequently used nonsystemic corticosteroid in the control group (76%). The age- and gender-specific fracture incidence in the control group was similar to that of the general population in GPRD.[1,32] The fracture incidence in a population sample of GPRD was 1.3 among men aged between 75 and 84 years and 3.0 among women of similar age.[1] In our control population, these figures were 1.2 and 2.7, respectively. For people aged 85 years or older, the GPRD population sample observed an incidence of 2.1 among men and 4.5 among women, as compared with 2.2 and 4.5, respectively, in our control population.

The baseline data for each NSAID taker was defined as the date of the first NSAID prescription after their practice's enrollment date in the GPRD. Each NSAID taker was followed from baseline until they sustained a fracture or until 91 days after the last NSAID prescription, or until the patient's change of practice, death, or the end of the study (whichever date came first). The period of 91 days after the last NSAID prescription was selected as it was considered likely that any fracture effects of NSAIDs would be transient. The control patients were followed from a randomly selected baseline date until the fracture, or until the patient's change of practice, death, or end of study. An analysis over the duration of NSAID use and an analysis of the reversibility of fracture risk after cessation of NSAIDs was conducted. In the reversibility analysis, each user who stopped therapy prior to the end of study was followed from 91 days after the last NSAID prescription until sustaining a fracture or being censored. Patients were included in this analysis whether or not they had sustained previous fractures. For the analysis of fracture risk prior to start of NSAID treatment, only patients who received their first NSAID prescription after the practice's enrollment date were included.

Cases consisted of patients who had a nonvertebral or vertebral fracture recorded in their medical records during follow-up. The classification of fractures was based on ICD-9 categories. In an earlier study, general practitioners were requested to confirm the diagnosis and to provide discharge summaries or diagnostic reports for 150 hip fracture and 150 vertebral fracture cases. Hip fracture was confirmed by the GP on the questionnaire in 91.0% of cases and by discharge summary in 85.2% of cases. Vertebral fracture was confirmed on the GP questionnaire in 88.1% of cases and by radiographic report in 76.3% of cases. According to the GPs, 96.4% of the vertebral fractures were diagnosed radiographically.[32] Factors associated with fractures and considered as potential confounding variables included diabetes mellitus, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anemia, dementia, depression, psychotic disorder, cerebrovascular accident, falls and a history of fractures, and back pain prior to baseline. Prescriptions during follow-up for anticonvulsants, methotrexate, thiazide diuretics, anxiolytics, antipsychotics, antidepressants, anti-Parkinson drugs, hormone replacement therapy, bisphosphonates, vitamin D, and calcitonin were also considered potential confounding variables.[10,27]

Statistical Methods

Incidence rates of fractures were calculated by dividing the number of patients with a fracture by the total number of patient-years of follow-up.[4] Adjusted relative rates were estimated using Cox proportional hazards models that included age, gender, and selected confounding variables. The final regression model was determined by backward selection using a significance level of 0.25.

Results

NSAIDs were prescribed to 501,427 patients. The cohort of regular NSAID users, who had received three or more NSAID prescriptions during follow-up, included 214,577 patients followed for a mean period of 3.4 years per person. The regular NSAID users were matched to a non-NSAID control group by gender and age (within 10 years); 78% of the regular NSAID users were matched by age (within 5 years), gender, and medical practice. The cohort of incidental NSAID users, patients who received only one or two NSAID prescriptions during follow-up, included 286,850 patients with an average follow-up of 0.7 years per person.

Table 1 summarizes the baseline characteristics of the comparison groups. The age and gender distributions of regular NSAID and non-NSAID control groups were similar: their mean age was around 54 years and 62.9% were women. The incidental NSAID group was younger (average age of 46 years) and included fewer women (58.9%). The non-NSAID control group reported a less frequent history of nonvertebral fractures compared with the regular NSAID users.

The rate of nonvertebral fractures was 1.0 fractures per 100 person-years in the non-NSAID control group, 1.5 in the incidental NSAID group, and 1.5 in the regular NSAID group (**Table 2**). After adjustment for potential confounding variables (coexisting disease, concomitant drug treatment, and a baseline history of fracture or back pain), the rate of nonvertebral fractures was significantly higher among regular NSAID users compared to non-NSAID control patients (relative rate [RR] = 1.47; 95% confidence interval [CI] 1.42–1.52). Among the most frequent fracture types (radius/ulna, carpal, tibia/fibula, hip, foot, and humerus), the highest excess incidence among the regular NSAID users compared with controls was found for carpal and foot fractures. The relative rates for these fractures were 1.66 (95% CI 1.52–1.83) and 1.62 (95% CI 1.47–1.79), respectively. The rate of nonvertebral fractures was comparable between regular and incidental NSAID users (RR = 1.04; 95% CI 0.99–1.09). Hip fracture rates were similar between the three groups. The relative rate of hip fractures in the regular NSAID group was 1.08 (0.98–1.19) compared with the non-NSAID control patients, and 1.05 (0.87–1.28) compared with the incidental NSAID users.

Figure 1 shows the age-specific incidence rates for nonvertebral fracture among men and women in the cohort according to their NSAID use. The regular NSAID users experienced higher rates of nonvertebral fractures compared with the control patients among men and women and at the different ages. Comparing the regular to incidental NSAID users, the adjusted relative rates were generally comparable between these two groups after adjustment for potential confounding variables. The only stratum that showed a statistically significant reduction in nonvertebral fractures was elderly women (aged ≥85 years) who were using NSAIDs regularly (RR 0.75; 95% CI 0.60–0.94). There was no

Table 1. Characteristics of comparison groups

	Regular NSAID users (n = 214,577)	Incidental NSAID users (n = 286,850)	Control group (n = 214,577)
Follow-up			
Total duration (person-years)	729,195	193,212	566,889
Mean duration of follow-up per subject (years)	3.4	0.7	2.6
Median duration of follow-up per subject (years)	3.2	0.2	2.3
Number of women	134,997 (62.9%)	169,015 (58.9%)	134,997 (62.9%)
Age (years)			
Mean	54.4	46.1	54.1
Median	55	44	55
Medical condition			
Back pain year before	41,536 (19.4%)	57,467 (20.0%)	6042 (2.8%)
Rheumatoid arthritis	4041 (1.9%)	953 (0.3%)	503 (0.2%)
Falls year before	2687 (1.3%)	3220 (1.1%)	1817 (0.8%)
Drug history in year prior to baseline			
Hormone replacement therapy	11,471 (5.3%)	13,080 (4.6%)	9929 (4.6%)
Fracture history in year prior to baseline			
Nonvertebral fracture	3336 (1.6%)	4296 (1.5%)	2247 (1.0%)
Vertebral fracture	232 (0.1%)	248 (0.1%)	73 (0.03%)

KEY: NSAID, nonsteroidal anti-inflammatory drugs.

difference in fracture rate between this group of regular NSAID users and the non-NSAID control group (RR 1.09; 95% CI 0.96–1.25).

The incidence of nonvertebral fractures stratified by NSAID type is shown in **Table 3**. It was found that the nonvertebral fracture rates were comparable between the three most frequently prescribed NSAIDs (ibuprofen, diclofenac, and naproxen). Users of indomethacin, mefenamic acid, and piroxicam had significantly lower rates of nonvertebral fracture compared with ibuprofen users. However, the reduced fracture rates may be explained by the following observations: significantly fewer women used indomethacin compared with ibuprofen (38.8% vs. 58.6%), and significantly younger patients used mefenamic acid (mean age 35.9 vs. 48.5 years). With respect to piroxicam, the rates of vertebral and hip fractures were comparable between piroxicam and ibuprofen (RRs 0.98 and 1.38, respectively). When restricting the analysis to elderly women (aged ≥65 years), no significant differences were found between the various NSAIDs in rate of fracture.

Figure 2 shows the incidence of fractures before, during, and after regular NSAID treatment. The incidence of nonvertebral fracture increased prior to baseline but decreased during regular NSAID treatment to a level within the baseline frequencies. The incidence of nonvertebral fractures was 1.7 cases per 100 person-years in the first year of treatment and 1.4 in the third year of treatment compared with baseline rates of 1.8 and 1.3. Following cessation of NSAID treatment, the fracture rates decreased toward baseline levels.

Discussion

The results of this study suggest that there are no differences in fracture risk between regular and incidental NSAID users. Regular NSAIDs users had a higher fracture risk compared with non-NSAID controls. Within the cohort of regular NSAID users, the fracture risks decreased over the duration of treatment, but this decrease did not fall below baseline levels.

Nonsteroidal anti-inflammatory drugs block inflammation by inhibiting the production of prostaglandin estradiol (PGE_2).[34] PGE_2 has been found to stimulate bone resorption and formation both in vitro and in vivo.[6,7,13,18,30] It has been hypothesized that NSAIDs may reduce the rate of bone loss, and thus prevent fractures, when bone resorption exceeds the bone formation.[19] Several animal studies reported prevention of bone loss,[8,19,29,36,37] although conflicting results have also been published.[16] There are limited data in humans on the effects of NSAIDs on bone metabolism. One study observed a 9% higher lumbar spine density among users of propionic acid NSAIDs.[24] Bauer et al. reported a 2.3%–5.8% increase in bone mass density of the hip and spine with daily use of aspirin or NSAIDs, whereas much smaller changes were observed with irregular drug use. However, no effects were on risk of fracture were observed with daily drug use.[3] These results conflict with data from earlier studies that found reductions in the risk of hip fracture.[26,28] In this study, no reductions were observed among regular NSAIDs users with regard to risk of fracture as compared with incidental NSAID users and non-NSAID controls. Our results are not

Table 2. Incidence of fractures by comparison group

	Control group		Incidental NSAID users		Regular NSAID users		Regular NSAID users vs. control group, adjusted relative rate (95% CI)	Regular NSAID users vs. incidental NSAID users, adjusted relative rate (95% CI)
	No. of cases	Rate (%)	No. of cases	Rate (%)	No. of cases	Rate (%)		
Nonvertebral	5793	1.0	2882	1.5	10,505	1.5	1.47 (1.42–1.52)	1.04 (0.99–1.09)
Forearm	1556	0.3	546	0.3	2516	0.3	1.33 (1.24–1.42)	1.07 (0.97–1.19)
Hip	686	0.1	140	0.07	973	0.1	1.08 (0.98–1.19)	1.05 (0.87–1.28)
Vertebral	192	0.03	208	0.1	808	0.1	2.90 (2.46–3.41)	1.22 (1.03–1.45)

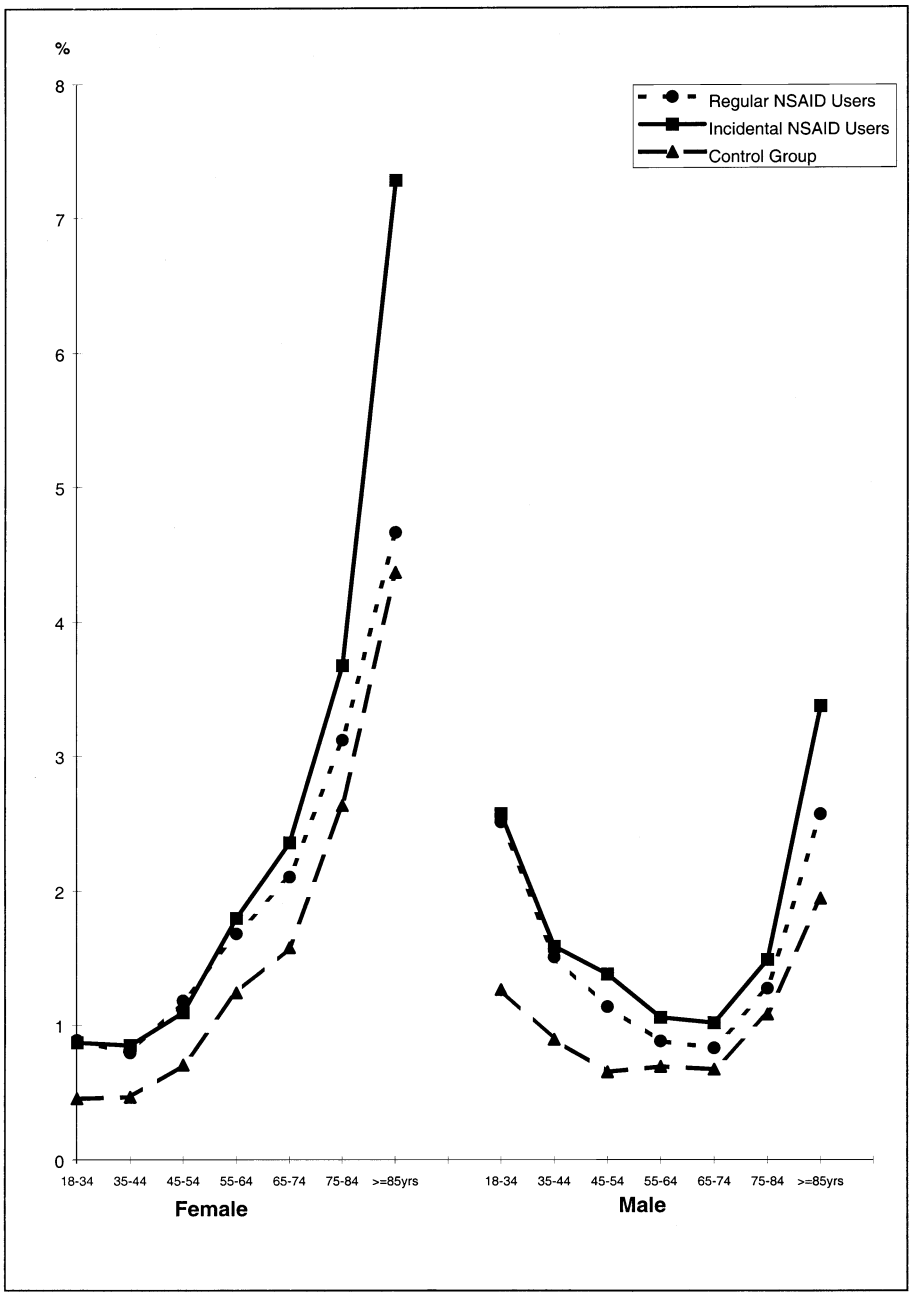

Figure 1. Annual incidence of nonvertebral fractures by age and gender.

supportive of NSAIDs substantively reducing the risk of fracture. In fact, the results show an increase in fracture rate among regular NSAID users compared with non-NSAID users. A possible explanation for this increase could be the underlying disease in NSAID users. When restricting the analysis only to patients with a history of arthropathy, the relative rate of nonvertebral fracture among regular NSAID users compared with control was reduced to 1.17 (95% CI 1.06–1.28).

Previous research found that there were differences between various NSAIDs in the degree of inhibition of prostaglandin-mediated bone resorption. In a mouse organ culture system, diclofenac was found to be a more effective inhibitor of prostaglandin synthesis in bone than indomethacin, which was more effective than piroxicam.[17] The results of this study do not confirm this bone potency ranking of NSAIDs. There were also no substantive differences between the NSAIDs with varying inhibition ratios of COX-1/COX-2. The effects of NSAIDs are through inhibition of enzyme cyclooxygenase (COX), of which two forms have been identified.[33] The hypothesis is that COX-2 is primarily responsible for prostaglandins produced in inflammation and COX-1 for prostaglandins in normal homeostasis.[23] Induction of COX-2 has been associated with prostaglandins produced by bone cells in response to mechanical stress and parathyroid hormone has been found to induce COX-2 expression in human osteoblasts.[9,21] In this study, more specific inhibitors of COX-2, such as naproxen and diclofenac,[33] did not show

Table 3. Incidence of nonvertebral fractures by NSAID type

Drug type	No. of cases	Rate	Adjusted relative rate (95% CI)
Ibuprofen	2400	1.6	Reference
Diclofenac	988	1.6	1.00 (0.93–1.08)
Naproxen	440	1.4	0.91 (0.82–1.00)
Indomethacin	169	1.3	0.81 (0.69–0.95)
Mefenamic acid	142	0.7	0.55 (0.46–0.66)
Piroxicam	105	1.2	0.72 (0.59–0.88)
Ketoprofen	101	1.5	0.88 (0.72–1.08)
Fenbufen	63	2.2	1.25 (0.97–1.61)

KEY: CI, confidence interval.

lower fracture risks than NSAIDs, which are predominantly COX-1 inhibitors (indomethacin or ibuprofen). There were also no consistent differences in fracture risks between propionic acid NSAIDs (such as ibuprofen and naproxen) and acetic acid NSAIDs (such as indomethacin and diclofenac). This contrasts with the results of a study in 114 NSAID users which found that regular use of propionic acid NSAIDs, but not acetic acid NSAIDs, was associated with substantively higher bone density.[24]

Our study has several possible limitations. The study was conducted in a cohort of subjects who received nonsystemic corticosteroids. This could have influenced the results if the NSAID effects were modified by prior or concomitant use of nonsystemic corticosteroids. However, exclusion of study patients with heavy use of nonsystemic corticosteroids did not modify the results. Another limitation of this study was that control for confounding was restricted to age, gender, and a variety of medical diagnoses and treatments. Other potential confounders, such as physical activity or baseline bone mass density, were not available. There was evidence to suggest that regular NSAID users had, on average, a higher baseline risk than the incidental NSAID users. The regular users included more elderly people and more patients with a history of rheumatoid arthritis. Thus, this bias could reduce the possibility of observing a small preventative effect of continuous NSAID use. There were major differences in the populations using the various NSAID types. The limited information on confounders did not allow for full adjustment of confounders in the analyses comparing the different NSAID types. Several analyses were conducted to review the sensitivity of the results to the method of analysis and control selection. Results did not materially change when adjustments were made for calendar year of follow-up or alcohol use, smoking, and body mass index, or when patients with peptic ulcer disease were excluded. Limiting the length of follow-up of control patients to the length of follow-up of the corticosteroid user also did not modify the results.

Our data are not supportive of clinically significant effects of NSAIDs on bone metabolism. There were no differences in fracture risk between regular and incidental NSAID users.

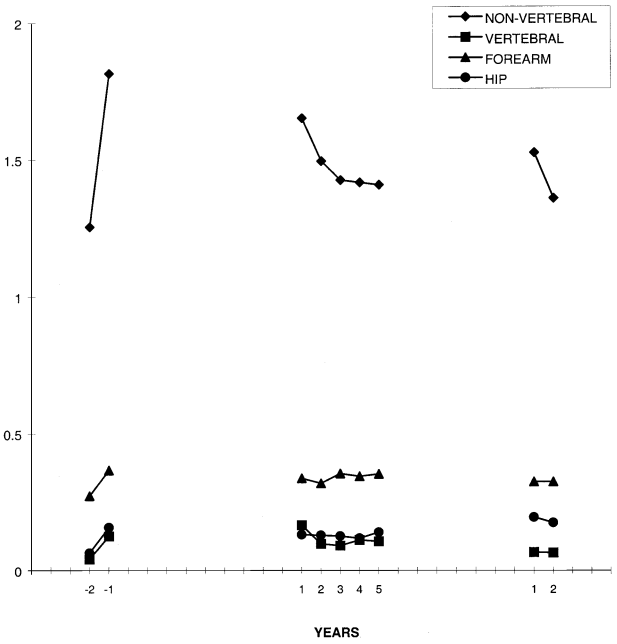

Figure 2. Incidence of fractures before, during, and after NSAID treatment (regular NSAID users).

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