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Original article

Comparison of conventional NSAIDs and cyclooxygenase-2 inhibitors in outpatients

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Abstract

***Objectives.* –** To compare outpatients treated with conventional nonsteroidal antiinflammatory drugs (NSAIDs) versus cyclooxygenase-2 (COX2) inhibitors in June 2002 in the Ain district of France.

***Patients and methods.* –** A cross-sectional study was done in the 14,216 patients older than 19 years of age who were identified in the universal health insurance database as having received therapy with conventional NSAIDs or COX2 inhibitors. A logistic regression model was built to identify factors associated with the type of antiinflammatory agent.

***Results.* –** COX2 inhibitor therapy was noted in 17% of patients. Factors significantly associated with COX2 inhibitor therapy were older age and concomitant use of symptomatic slow-acting drugs for osteoarthritis, disease-modifying antirheumatic drugs, anticoagulants, antiplatelet agents, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II receptor antagonists. Patients taking COX2 inhibitor therapy were significantly less likely to be taking concomitant gastroprotective therapy, compared to patients on conventional NSAIDs.

***Conclusions.* –** The powerful advertisement campaigns that surrounded the introduction of COX2 inhibitors rapidly affected practice patterns regarding the prescription of antiinflammatory drugs. The study reported here showed a significantly greater likelihood of receiving COX2 inhibitors in older patients taking multiple medications, a population known to be at increased risk for drug-induced cardiovascular events. Evidence obtained after the present study established that COX2 inhibitors carry a risk of cardiovascular side effects. Rofecoxib has been removed from the market, and new recommendations have been issued regarding other COX2 inhibitors.

Keywords: NSAID; COX2 inhibitors; Nonsteroidal antiinflammatory drugs; Cyclooxygenase-2 inhibitors

1. Introduction

Selective cyclooxygenase-2 (COX2) inhibitors block the activity of the COX2 cyclooxygenase isoform [1] but spare the COX1 isoform, which ensures normal production of prostaglandins that protect the gastrointestinal tract. COX2 inhibitors were developed in an attempt to improve the gastrointestinal safety profile of nonsteroidal antiinflammatory drugs (NSAIDs) [2,3]. They were introduced in France in September 2000, and in June 2002 two COX2 inhibitors were available, celecoxib and rofecoxib. Both drugs were approved for alleviating symptoms in patients with osteoarthritis or rheumatoid arthritis [4–6]. Clinical trials in these two conditions showed that improvements in pain and function were similar to those obtained with nonselective NSAIDs (NS-NSAIDs) [7–9]. However, the risk of serious gastrointestinal events was reduced by about 50% [2,10–12]. Nephrotoxicity is a feature shared by COX2 inhibitors and NS-NSAIDs [13–17]. Furthermore, studies conducted after the introduction of COX2 inhibitors showed an increased risk of cardiovascular adverse events. These new findings led to removal of rofecoxib from the French market in September 2004 and to recommendations limiting the use of celecoxib [2,18–20]. In contrast to NS-NSAIDs, COX2 inhibitors have no antiplatelet effects when used in therapeutic dosages [12].

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Concomitant use of other medications worsens the adverse effects of NSAIDs. For instance, concomitant use of a vitamin K antagonist or of another NSAID (including aspirin in a dosage greater than 3 g/day) increases the risk of bleeding, and this effect is greatest in the oldest patients. Similarly, concomitant use of heparin or an antiplatelet agent requires special caution. Hyperkalemia and acute renal failure may develop in older individuals and patients with dehydration who take an angiotensin II receptor antagonist, an angiotensin-converting enzyme (ACE) inhibitor, or a diuretic concomitantly with an NSAID [21]. Because COX2 inhibitors spare the constitutively expressed COX1 isoform, physicians probably use them in patients who differ in terms of age, comorbidities, and concomitant medications from those given NS-NSAIDs. To investigate this hypothesis, we compared outpatients given COX2 inhibitor therapy to those given NS-NSAIDs in June 2002 in a well-defined geographic region of France. At the time of the study, COX2 inhibitors had not yet been recognized as inducing adverse cardiovascular events and were widely viewed as safer than NS-NSAIDs.

2. Patients and methods

2.1. Population

We conducted a cross-sectional study using the main universal health insurance database for the Ain district of France. About 16.6% of residents in the Ain district receive health insurance through branches of the universal health insurance system that do not enter data into the main database. Thus, our source population was about 83.4% of the 515,000 individuals residing in the Ain district at the time of the study [22]. Nearly all prescription medications are reimbursed. In the main database, medications delivered to outpatients by pharmacies are identified by seven-digit bar codes. Medications purchased over the counter or administered to inpatients are not in the database; also missing are the few prescription medications not reimbursed by the universal health insurance system [23]. We identified patients who were recorded in the main database as being older than 19 years of age and having claimed reimbursement for an NS-NSAID or COX2 inhibitor between June 1 and June 30, 2002.

2.2. Variables

For each patient, we recorded, age, sex, whether NS-NSAID or COX2 inhibitor therapy was prescribed and the date prescribed, the date a gastroprotective agent was prescribed (where applicable), and whether medications known to carry safety risks when used concomitantly with NS-NSAIDs or COX2 inhibitors were prescribed also. These medications were anticoagulants, antiplatelet agents, aspirin in a dosage of 500 mg or more, diuretics, ACE inhibitors, and angiotensin II receptor antagonists. We also recorded concomitant use of symptomatic slow-acting drugs for osteoarthritis (Sy-SADOA), disease-modifying antirheumatic drugs (DMARDs), glucocorticoids, and gastroprotective agents. The list of proprietary medications used was drawn up according to the French Drug Compendium (Vidal dictionary) and to the classification developed by the European Pharmaceutical Market Research Association. Interactions were identified by the Drug Interactions Task Force (GTIAM) at the French Agency for Healthcare Product Safety (AFSSAPS) [24].

2.3. Statistics

The chi-square test was used to compare rates of occurrence and the Student's *t*-test to compare means. Variables independently associated with use of a COX2 inhibitor rather than an NS-NSAID were identified by multivariate logistic regression with computation of the adjusted odds ratio (aOR) and 95% confidence interval (95%CI). *P* values no greater than 0.05 were considered significant. SPSS, version 11.0 was used to perform all statistical tests.

3. Results

3.1. Characteristics of patients with NSAID prescriptions

Of the 14,216 patients identified in the database as having received a NSAID prescription in June 2002 in the Ain district, 83% were given an NS-NSAID and 17% a COX2 inhibitor. Patient characteristics are reported in Table 1. Women predominated in both groups, but the female predominance was significantly more marked in the COX2 inhibitor group that in the NS-NSAID group in the univariate analysis ($P < 0.001$). Other factors significantly associated with COX2 inhibitor use in the univariate analyses were older age and concomitant medications. Mean age was significantly higher in the COX2 inhibitor group ($P < 0.001$), the difference with the NS-NSAID group being about 14 years (60 vs. 46.2 years). Fig. 1 shows the proportions of patients in each treatment group by age group; the proportion of patients older than 65 years was 20% in the NS-NSAID group and 40% in the COX2 group. Use of concomitant medications other than gastroprotective agents was more common in the COX2 inhibitor group. Patients in the NS-NSAID group were significantly more likely to receive gastroprotective therapy than those in the COX2 inhibitor group ($P < 0.04$). Gastroprotective therapy was significantly less common among women in the COX2 inhibitor group than among women in the NS-NSAID group ($P = 0.05$) (Table 2).

Variables independently associated with COX2 inhibitor use in the multivariate model are reported in Table 3. Compared to the NS-NSAID group, patients in the COX2 inhibitor group were significantly more likely to be taking Sy-SADOAs, DMARDs, diuretics, ACE inhibitors, or angiotensin II receptor antagonists. In contrast, patients in the COX2 inhibitor group were significantly less likely to be taking gastroprotective therapy.