NSAID Usage: Impact of Safety Data and Product Withdrawals on Prescribing Trends

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ABSTRACT

Purpose. This article characterizes trends in prescribing nonsteroidal anti-inflammatory drugs (NSAIDs) following the withdrawal of rofecoxib (Vioxx) and valdecoxib (Bextra) from the market.

Methods. A retrospective claims analysis evaluated NSAID prescription claims dispensed from a national retail pharmacy chain for a single insurance company covering 521,534 lives from April 1, 2004, to June 30, 2005. NSAIDs were classified as nonselective or cyclooxygenase-2 (COX-2)–selective.

Results. During the 18-month period studied, a total of 2.9 million prescriptions were dispensed; 83,784, or 2.9% of these, were for NSAIDs. Before October 2004, COX-2 prescriptions had accounted for 37% of the total NSAID prescriptions dispensed (2,299 per month); between April 2005 and June 2005, COX-2s represented 16% of the prescriptions filled (775 per month). The number of nonselective NSAID prescriptions remained relatively constant at slightly more than 3,000 per month, until an increase of almost 33% occurred (to more than 4,000 per month) between April 2005 and June 2005.

The number of ibuprofen prescriptions remained relatively stable, and there were modest increases for most other nonselective NSAIDs after September 2004. Prescriptions for meloxicam (Mobic) more than doubled—from an average of 127 per month before October 2004 to a high of 330 in June 2005.

Conclusion. Physician-prescribing patterns for NSAIDs showed a rapid response to the release of postmarketing safety data and subsequent withdrawal of two COX-2–selective NSAIDs from the market.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used classes of medications, accounting for 3% of all prescriptions dispensed in the U.S.1–3 About 50 million Americans receive NSAID therapy for both chronic disorders, including rheumatoid arthritis and osteoarthritis, and acute conditions such as postoperative pain, headache, tendonitis or bursitis, and dysmenorrhea.4,5

All NSAIDs inhibit the COX enzymes responsible for prostaglandin (PG) synthesis, but the COX-2–selective agents, as compared with COX-1, preferentially inhibit COX-2.4–7 The COX-1 enzyme is constitutively expressed and primarily maintains homeostatic function, especially in the gastrointestinal (GI) tract, platelets, and kidneys. COX-2 is an inducible enzyme in inflammatory states, but it is also expressed in small amounts in certain tissues, including the kidney, brain, and bone, when no apparent inflammation is present. Therefore, it is generally accepted that the risk of GI toxicity is reduced when COX-2–selective NSAIDs are used.8,9

The introduction of the COX-2–selective NSAIDs—celecoxib (Celebrex, Pfizer), and rofecoxib (Vioxx, Merck)—to the U.S. market in 1999 led to an increase of almost 50% in the total number of NSAID prescriptions dispensed.1 The number of prescriptions increased from 62 million (in 1998) to 92 million (in 1999), with COX-2 drugs accounting for two thirds of this increase. A third COX-2–selective NSAID, valdecoxib (Bextra, Pharmacia/Pfizer), became available in 2001, but it had little effect on the total number of COX-2 drugs prescribed annually.10

Recent reports of adverse effects associated with the use of COX-2–selective and some nonselective NSAIDs, followed by the market withdrawal of rofecoxib (in late 2004) and valdecoxib (in 2005), have influenced clinicians to change their prescribing practices.11–15 Our goal in this article is to characterize NSAID usage before and after the withdrawal of rofecoxib and valdecoxib from the market.

METHODS

Health insurance claims data were analyzed to assess changes in NSAID prescribing trends. The database comprised dispensing claims from a national retail pharmacy chain for a single insurance company in the northwestern and northeastern New York regions from April 1, 2004, through June 30, 2005. Forty

Disclosure: Although Dr. Ansani, a Pfizer employee, was involved in the analysis and preparation of the manuscript, Pfizer (the manufacturer of celecoxib and valdecoxib) did not provide any monetary funding, including grants or sponsorships, for this research. The research in this article was presented, in part, at the American College of Rheumatology Clinical Meeting in San Diego, California, in November 2005.
percent of the 521,534 beneficiaries received their medications through this pharmacy chain, which used a tiered formulary.

We analyzed total prescription claims data, evaluating NSAID use and stratifying the analysis according to nonselective or COX-2–selective NSAIDs. We then examined prescription data for the six months prior to rofecoxib’s withdrawal (from April to September 2004) through the nine months following its withdrawal (from October to June 2005) to assess trends in prescribing patterns. Unless otherwise indicated, we used the average of the monthly data for the period April to September 2004 as the baseline for comparison with subsequent monthly data. It was not possible to track the over-the-counter NSAIDs.

RESULTS

During the period studied, 2.9 million prescriptions were dispensed; 83,784 (2.9%) were for NSAIDs: 24,377 were for COX-2–selective NSAIDs (29%), and 59,407 were for nonselective NSAIDs (71%). From April to September 2004, an average of 2,299 prescriptions for COX-2–selective NSAIDs were dispensed each month.

Following the withdrawal of rofecoxib (in late September 2004) and valdecoxib (in April 2005), this number dropped steadily during the successive three-month periods—from October to December 2004, from January 2005 to March 2005, and from April 2005 to June 2005—to monthly averages of 1,632, 1,122, and 775 prescriptions, respectively. By the beginning of 2005, the total number of NSAID prescriptions dispensed had decreased by 22% (Figure 1).

During the same three-month time periods, the number of nonselective NSAID prescriptions remained relatively constant, at slightly more than 3,000 per month, until the third three-month time period (April 2005 to June 2005), when an increase of almost 33% occurred (to more than 4,000 per month).

Before October 2004, the COX-2–selective agents had accounted for 37% of all of the NSAID prescriptions dispensed. Beginning in October 2004, the total number of NSAID prescriptions decreased, primarily because of a reduction in the number of prescriptions for COX-2–selective NSAIDs. The COX-2 agents, therefore, were a progressively smaller proportion of total NSAID prescriptions dispensed throughout the time studied, and this number decreased to 16% of the total number of NSAID prescriptions for the final three-month time period studied (from April 2005 to June 2005).

During the 15 months studied, the number of ibuprofen prescriptions remained relatively stable, and there was a modest increase (from 12% to 25%) for most other nonselective NSAIDs after rofecoxib was removed from the market (Figure 2). However, the percentage of prescriptions for meloxicam (Mobic, Boehringer Ingelheim) increased by 160%, from an average of 127 prescriptions per month (from April 2004 to September 2004) to a high of 330 in June 2005.

The number of prescriptions for celecoxib and naproxen sodium (Anaprox, Naprosyn, Roche) temporarily increased; however, after the Food and Drug Administration (FDA) issued advisories and news releases in late 2004, this number decreased by 38% and 20%, respectively (Figure 2).

DISCUSSION

Our study indicates that the release of adverse postmarketing safety information in late 2004 and early 2005 dramatically influenced prescribing patterns for NSAIDs. Although the total number of prescriptions dispensed for NSAIDs has decreased overall since the fall of 2004, most of this decrease was attributable to a 66% reduction in prescriptions for the COX-2–selective NSAIDs.

Although the efficacy of COX-2–selective agents is similar to that of the traditional NSAIDs, their GI side effects are fewer in number.1–5 Adverse cardiovascular side effects—primarily nonfatal myocardial infarction (MI)—were noted with rofecoxib 50 mg once daily, compared with the usual doses of naproxen (500 mg twice daily), as early as 2000, with the publication of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.6

![Figure 1: Total number of prescriptions for COX-2–selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) dispensed between April 1, 2004, and June 30, 2005.](image-url)
However, the Celecoxib Long-term Arthritis Safety Study (CLASS) found no increase in cardiovascular side effects with celecoxib 400 mg twice daily, compared with the usual doses of either diclofenac potassium (Cataflam, Novartis) or ibuprofen.9

Retrospective claims data analyses also demonstrated an elevated cardiovascular risk with rofecoxib, especially at high doses, but not with celecoxib.16–20 Published data relating specifically to the changes in NSAID prescribing trends that we describe (see Figure 2) are summarized next.

In September 2004, the Data Safety Monitoring Board of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial reported an increase in cardiovascular events with rofecoxib.21 Merck stopped the trial early. On September 30, 2004, the company voluntarily withdrew rofecoxib from the market.22 In November 2004, greater cardiovascular toxicity was noted in patients after coronary artery bypass graft (CABG) surgery who were given parecoxib, an injectable pro-drug of valdecoxib and oral valdecoxib when compared with patients receiving placebo.23 These findings led to a contraindication in the valdecoxib label for the treatment of postoperative pain immediately following CABG surgery, and they resulted in a boxed warning for the product.24,25

In December 2004, subsequent data from two similar placebo-controlled poly-p-revention trials with celecoxib were contradictory in terms of their cardiovascular side effects.26,27 The Adenoma Prevention with Celecoxib (APC) trial was terminated early because of a dose-dependent increase in composite endpoint of death from cardiovascular causes, MI, stroke, or heart failure in subjects taking celecoxib compared to those taking placebo.26 However, results of the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial did not show an increase in cardiovascular events in subjects taking celecoxib compared with those taking placebo.27

In December 2004, the FDA also reported the termination of a National Institutes of Health (NIH) study that was using naproxen, celecoxib, or placebo to treat elderly patients at risk for Alzheimer’s disease, the Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT). A preliminary analysis indicated an increased risk of cardiovascular events in the naproxen-treated subjects compared with those treated with placebo and suggested no difference between placebo and celecoxib.28

In February 2005, the FDA convened an Arthritis Advisory Council Committee to evaluate all published and non-published information and to make recommendations regarding the marketability, labeling, and overall safety of the COX-2–selective NSAIDs coxib drugs.29,30 On April 6, 2005, the FDA decided that the data did “not clearly demonstrate that the COX-2–selective agents confer a greater risk of serious adverse CV events than nonselective NSAIDs.”31 The Agency also found that both selective and non-
selective NSAIDs demonstrated an increased risk, compared with placebo, but it was unable to rank the drugs with respect to cardiovascular risk.

The FDA recommended a black-box label for all prescription NSAIDs to include warnings of both cardiovascular and GI risk; they also recommended an expanded warning for over-the-counter NSAIDs, including GI bleeding risk, cardiovascular risk, and serious skin reactions. The agency also requested the voluntary withdrawal of valdecoxib because of an increase in reports of serious skin reactions, including Stevens–Johnson syndrome, compared with other selective NSAIDs and all nonselective NSAIDs.25,28

STUDY LIMITATIONS

Some limitations of our study included the retrospective nature of the claims data, which were restricted to prescribing in New York State. These data also included fewer than half of the pharmacy beneficiaries of an insurance company, and we could not track over-the-counter NSAID use.

Data were available only through June 2005. An additional analysis of prescription claims data beyond this time, as well as the findings from subsequent publications, would be helpful to quantify the sustained impact of these events on overall NSAID use.

CONCLUSION

Our data demonstrate the effect of adverse events on NSAID prescribing in northern New York State. Celecoxib use increased following the removal of rofecoxib from the market (Figure 2) but then decreased sharply as concerns were raised following the release of the APC trial results. Similarly, naproxen use fell after the NIH terminated its Alzheimer’s disease study (ADAPT).

The use of other NSAIDs, which had received no adverse publicity—the cardiovascular risk has not been investigated in most of these drugs—either increased or remained unchanged. These monthly changes in prescribing patterns reflect the responses of clinicians, health care systems, the pharmaceutical industry, and consumers to these series of events.

REFERENCES