Relative Value of the NSAIDs, Including COX-2 Inhibitors and Meloxicam

The potential value of selective inhibition of the cyclooxygenase 2 (COX-2) enzyme was described by Klein et al. in October 1994. Within 14 months, by year-end 1995, there were 113 articles indexed by PubMed on the subject of COX-2 inhibition. A search of PubMed using the term “COX-2” conducted in March 2006 yielded 8,833 citations. The initial enthusiasm for potential gastrointestinal (GI) protection associated with COX-2 enzyme inhibition gave way to criticism of the apparent insignificant effect in GI protection and evident cardiovascular risk, particularly compared with the nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). Ortiz summarized much of the evidence on the subject of the relative value of the COX-2 inhibitors versus NSAIDs following the U.S. market withdrawal of rofecoxib on September 30, 2004.

In the September 2005 issue of JMCP, Stockl et al. found that users of COX-2 inhibitors did not have a reduced risk of GI bleed events compared with users of NSAIDs who had similar baseline characteristics. In that study of 35,007 pairs of COX-2 inhibitor and NSAID users, there were 375 cases of GI bleed among 19,201 follow-up years for COX-2 users, or 19.5 cases per 1,000 person-years, versus 228 cases of GI bleed among 12,680 follow-up years for NSAID users, or 18.0 cases per 1,000 person-years. There was no difference in the risk of GI bleed for COX-2 versus NSAID users (relative risk 1.07; 95% confidence interval [CI], 0.90-1.26), and even among high-risk patients, the relative risk of a GI bleed for COX-2 inhibitor users was 0.995 (95% CI, 0.84-1.19).

In December 2005, Hippisley-Cox et al. found that the use of naproxen, diclofenac, and rofecoxib (Vioxx) but not celecoxib (Celebrex) was associated with increased risk of an upper GI event, defined as peptic ulcer or hematematosis. The adjusted odds ratios were 2.12 (95% CI, 1.73-2.58) for naproxen, 1.96 (95% CI, 1.78-2.15) for diclofenac, 1.56 (95% CI, 1.30-1.87) for rofecoxib, and 1.11 (95% CI, 0.87-1.41) for celecoxib. While Stockl et al. matched COX-2 inhibitor users with nonselective NSAID users, Hippisley-Cox et al. matched COX-2 or NSAID users with a first-ever diagnosis of upper GI event with controls matched for age, sex, calendar time (between August 1, 2000, and July 31, 2004), and practice (among 367 general practices in the United Kingdom). Like Stockl et al., Hippisley-Cox et al. concluded that there was no consistent evidence of protection from GI events for the COX-2 inhibitors compared with nonselective NSAIDs.

Two congruent findings in 2 different countries involving 70,014 patient records in Stockl et al. and 98,274 patient records in Hippisley-Cox et al. for the same approximate time period provide additional evidence of the apparent lack of value of COX-2 inhibitors in preventing or reducing the incidence of adverse upper GI events. In October 2005, between the publication dates for Stockl et al. in September and Hippisley-Cox et al. in December, Abraham et al. concluded from their review of 303,787 high-risk Veterans Administration patients that only 27.2% (n = 82,766) were prescribed NSAIDs safely in 2002, based on “evidence-based guidelines.” Abraham et al. defined guideline adherence as the coincident use of gastroprotection with a nonselective NSAID or use of a COX-2 inhibitor in high-risk patients. A high-risk patient was aged 65 years or older, used a corticosteroid or anticoagulant concurrently, had a history of peptic ulcer, or had a high average daily dose of NSAIDs (e.g., 1,500 mg per day of naproxen, 200 mg per day of diclofenac, or 2,400 mg per day of ibuprofen). An interesting question not addressed by Abraham et al. has to do with the unnecessary use of COX-2 inhibitors in patients not at risk of upper GI events. Johns et al. found that 81% of the users of COX-2 inhibitors were not in the high-risk category for upper GI events.

Further, the evidence supports the use of alternatives to the COX-2 inhibitors in patients at elevated risk of a GI bleed. Chan et al. established that omeprazole 20 mg per day plus diclofenac 75 mg twice daily was comparable to celecoxib 200 mg twice daily in the incidence of recurrent GI bleed in patients at high risk for GI bleed, after accounting for coincident aspirin use and status of infection with Helicobacter pylori. Setting aside the potential for adverse cardiovascular events associated with COX-2 inhibitors, the availability of over-the-counter omeprazole (Prilosec OTC) means that it is possible in 2006 to treat 4 patients at high risk of a GI event with omeprazole 20 mg daily plus 75 mg diclofenac twice daily for the same cost ($1.32 per day per patient, Table 1) for each high-risk patient treated with celecoxib 200 mg twice daily ($5.28 per day per patient).

The market withdrawal of rofecoxib on September 30, 2004, created an opportunity for another nontraditional NSAID—meloxicam (Mobic)—touted by some as a “COX-1.” It is probably no coincidence that meloxicam, an NSAID not caught up directly in the COX-2 inhibitor controversy, led the price increases for all brand name drugs in January 2005. The manufacturer raised the price of the meloxicam 7.5 mg tablet by 7% and by 11% for the more commonly used 15 mg tablet.

Despite the same label warning as other NSAIDs regarding cardiovascular risk and GI risk, meloxicam leads the NSAID drug class in 2006 in average cost per 30-day supply. Discount prices in March 2006 for a standardized 30-day supply were $124 for meloxicam 15 mg per day and ranged from $79 for 1 capsule of celecoxib 200 mg per day or $158 per month for 2 capsules per day (Table 1). Comparing these prices with actual managed care organization (MCO) prices regardless of drug strength showed that meloxicam had an average MCO cost (before rebate and before member cost-share) of $132 per 30-day supply in early 2006. Approximately half of the pharmacy claims and half of total days of meloxicam therapy are accounted for by the 15 mg tablet, with an average of 1.02 tablets per day. The other half of meloxicam pharmacy claims and total days of therapy.
therapy in 2006 are for the 7.5 mg tablet, with an average of 1.35 tablets per day.11 The average actual MCO cost for celecoxib was $113 per 30-day supply in early 2006 (an average of 1.33 units per day), suggesting that actual use involves a mixture of celecoxib strengths (100 mg, 200 mg, or 400 mg capsules) and either 1 or 2 capsules per day. Therefore, in actual use, meloxicam had a price premium of 15% compared with celecoxib in the first 3 months of 2006.

In order to understand better why the U.S. market embraced meloxicam in 2005 and 2006, it is helpful to recall the regulatory history of the COX-2 inhibitors. On September 30, 2004, the U.S. Food and Drug Administration (FDA) requested the market withdrawal of rofecoxib (Vioxx) due to safety concerns associated with an apparent increased risk of cardiovascular events, particularly heart attack and stroke.12 Six months later, on April 7, 2005, the FDA asked the manufacturer of valdecoxib (Bextra) to voluntarily withdraw the drug from the market.13 Steve Galson, acting director of the FDA Center for Drug Evaluation & Research, said that, at the time, there was “no added advantage, and a special risk,” in the higher rate of adverse skin reactions with Bextra, and “the cardiovascular risks of these drugs are what we consider a class effect.”14

The media attention surrounding the market withdrawal of these two COX-2 inhibitors and the ensuing litigation against the manufacturer of rofecoxib alleging patient harm was associated with a 40% slide in celecoxib sales in 2005 (Figure 1); celecoxib dropped from rank #6 in total community pharmacy sales in 2003 to rank #26 in 2005. The decline in sales of celecoxib was picked up, in large part, by a 118% increase in meloxicam sales in 2005. Meloxicam rose from rank #111 in total expenditures in 2003 to rank #26 in 2005. The decline in sales of celecoxib was picked up, in large part, by a 118% increase in meloxicam sales in 2005. Meloxicam rose from rank #111 in total expenditures in 2003 to rank #38 in 2005.

The plummeting sales of the COX-2 inhibitors as a class have resulted mostly from the attention of the public and health care professionals to the apparent increased cardiovascular risk, not primarily from failure to protect patients from adverse GI events. Comparison of the adverse event data across all NSAIDs and COX-2 inhibitors shows a low incidence of myocardial infarction (<1%) for all NSAIDs except tolmetin (3%-9%), rofecoxib (3.5%-10%), valdecoxib (1.6%-2.1%), celecoxib (<2%), and meloxicam (<2%).15

In the assessment of relative value of COX-2 inhibitors versus NSAIDs, it is important to remember that the FDA (a) allowed the manufacturer of rofecoxib (Vioxx) to add to its product label the results of the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial that suggested a GI protective effect compared with naproxen,16 although subsequent controversy swirled years later, in 2005 and 2006, surrounding the selective omission of 3 deaths of patients who took rofecoxib17; (b) never permitted a claim of less GI harm for any NSAID or COX-2 inhibitor except rofecoxib; and (c) rejected the request from the manufacturer of celecoxib to drop the warning of possible GI adverse effects from the label.18
Disappointment would be in store for those who assume that there is clinical evidence of the superiority of meloxicam over the traditional NSAIDs in GI protection. The early clinical trials (the drug was approved by the FDA for use in arthritis patients on April 14, 2000) suggested that meloxicam was equal in efficacy to traditional NSAIDs and may have some advantage in GI protection. For example, the manufacturer sponsored a study of 774 patients with osteoarthritis of the hip or knee and a flare that concluded that meloxicam had a lower rate of GI adverse events compared with diclofenac, but this difference was not for bleeding events; rather, it was for all GI adverse events such as nausea and diarrhea. Also, this study by Yocum et al., like the other clinical trials used to obtain FDA approval of meloxicam, was of short duration—only 12 weeks. It is also noteworthy that Yocum et al. pooled the adverse GI event data for all 3 doses of meloxicam, including the 3.75 mg dose per day that did not prove superior in efficacy to placebo.

Later, in a meta-analysis of data from randomized, controlled trials (RCTs) published through January 2003, Richy et al. found that meloxicam had possible superiority to both naproxen and diclofenac in relative risk of GI complications for NSAID users compared with nonusers, but the risk of GI complications was not different for meloxicam users versus NSAID users compared with nonusers, the risk of GI adverse events such as nausea and diarrhea. Also, this study by Yocum et al., like the other clinical trials used to obtain FDA approval of meloxicam, was of short duration—only 12 weeks. It is also noteworthy that Yocum et al. pooled the adverse GI event data for all 3 doses of meloxicam, including the 3.75 mg dose per day that did not prove superior in efficacy to placebo.

In conclusion, it is possible to treat 3 to 4 patients with therapeutically equivalent regimens of naproxen plus omeprazole OTC or diclofenac plus omeprazole OTC for the total cost equivalent to treat 1 patient with celecoxib. Drawing upon the research of Johnsen et al. in which only 19% of users of COX-2 inhibitors were at increased risk of a GI bleed, 81% of the use of celecoxib could have been either naproxen or diclofenac or other traditional NSAIDs and 19% could have been omeprazole OTC and either naproxen or diclofenac, at lower cost (Table 1). Applying these ratios of use of therapeutically equivalent, lower-cost therapies, consumers and third-party payers over-spent by $4.45 billion on celecoxib over the last 3 years. Since there is no evidence of the superiority of meloxicam over other NSAIDs, overspending on meloxicam in the United States was $1.38 billion over 3 years, a total avoidable waste of $5.83 billion. Surely, we could have found better use for this money.

So, this is another example of cheaper is better. Evidence-based medicine supports the use of the lower-cost therapies, including omeprazole plus either naproxen or diclofenac, over the use of celecoxib in patients at increased risk of upper GI bleed. Regarding meloxicam, when it becomes equivalent in price to its NSAID clinical peers, perhaps it will be a reasonable choice for formulary inclusion, but for now it is an expensive COX-2 pretender in “the Emperor’s new clothes.”

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### REFERENCES


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