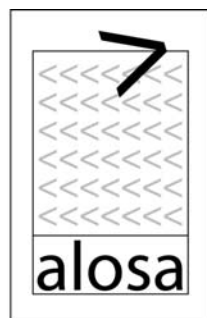


NSAIDs and Cox-2 Inhibitors: What Now?

A review of the evidence for the practicing physician



The Alosa Foundation



Balanced data about medications

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The Independent Drug Information Service (iDiS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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October 2005

Introduction

Over the past year, several events have caused physicians and patients to question their basic assumptions about the benefits and risks of pain medications. In September 2004, Merck announced that in a trial^{1,2} it was conducting, patients taking Vioxx (rofecoxib) had serious cardiovascular complications (including myocardial infarction [MI] and stroke) at twice the rate of trial patients given placebo; the drug was immediately withdrawn from the market. Not long after, another large randomized trial found that high-dose Celebrex (celecoxib) caused a doubling or tripling of the risk of serious cardiovascular outcomes in patients given that drug rather than placebo – although that finding was not replicated in another large randomized trial of Celebrex. During this period, the third cox-2 inhibitor, Bextra (valdecoxib), was discovered to cause two-fold to nearly four-fold elevations in serious cardiovascular outcomes (including deaths) in a trials that compared it with placebo;³ that drug too, was withdrawn from the market.

The situation became even more complex in April 2005 when the Food & Drug Administration warned physicians and the public that the increased risk of cardiac events seen with the cox-2 inhibitors might also be caused by most older non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (e.g., Motrin), naproxen, and all similar drugs. It ordered that **all** products in this class be labeled as carrying an increased risk of cardiovascular disease. Patients all over the country anxiously called their doctors to find out whether they should stop taking medications that some of them had been using for decades. Unfortunately, neither the FDA nor the manufacturers had satisfactory answers to these questions.

When they were first approved by FDA in 1999 after fast-track review, the cox-2 inhibitors Celebrex and Vioxx were seen by many as a major breakthrough in analgesia, promising excellent pain-relieving and anti-inflammatory efficacy with diminished gastrointestinal toxicity. But in 2004-2005, awareness that these drugs could double or triple the risk of MI, stroke, and other serious outcomes brought new scrutiny to the two other main properties of the class: their comparative analgesic efficacy and their risk of gastrointestinal hemorrhage. Clinicians, patients, and policymakers were forced to consider difficult questions such as “Is some gastroprotection worth a greater risk of MI or stroke?” “How



much pain relief would be worth an increased chance of death?" Many papers have been published on these questions, and even more data is available at the FDA website and from other sources that are not in the medical literature. This overview is designed to provide the practicing physician with an unbiased, evidence-based overview of these issues. The goal is to answer practical prescribing questions, so as to provide patients with the most effective analgesic regimens while minimizing their risk. It synthesizes the available information in clinically relevant terms, and will cover the following four areas:

- comparative analgesic efficacy of the NSAIDs and coxibs;
- how to reduce the gastrointestinal side effects of these drugs;
- the relative cardiovascular safety of currently available NSAIDs and the one remaining cox-2 inhibitor;
- cost-effectiveness considerations.

Analgesic Efficacy

"The American College of Rheumatology notes that acetaminophen is comparable in effectiveness to NSAIDs for many patients, and recommends an adequate trial of this drug before resorting to an NSAID."⁴

With the heavy promotion of NSAIDs and coxibs, it is important to keep in mind that for many people with non-severe acute or chronic pain, acetaminophen (Tylenol, etc.) often provides satisfactory pain relief. It poses no risk of gastrointestinal hemorrhage, and there is no evidence that it increases the risk of myocardial infarction or stroke. Many rheumatologists and pain experts suggest it as a first-line treatment, and the American College of Rheumatology (ACR) and its European counterpart both recommend acetaminophen as the first-line drug for analgesia in patients with osteoarthritis.^{4,5} The ACR notes that acetaminophen is comparable in effectiveness to NSAIDs for many patients, and recommends an adequate trial of this drug before resorting to an NSAID. Similarly, the society of European rheumatologists considers acetaminophen the oral analgesic of first choice for mild to moderate pain, and the preferred analgesic for long-term use. Total daily dose of acetaminophen should not exceed 4g/d (two 500 mg tablets q.i.d.), or 3 g/d in patients over 65 to help prevent hepatotoxicity. The drug should be avoided in alcoholics, patients who

are fasting, or those with liver disease or uncontrolled hypertension.⁶ If acetaminophen is inadequate when used alone, it is still useful to retain it in the analgesic regimen so that additional drugs can be prescribed at lower doses.

“There is virtually no evidence that any of the available NSAIDs or cox-2 inhibitors have greater analgesic efficacy overall than any other.”⁷

When acetaminophen is not enough, one must make a choice within the NSAID category, ranging from some of the oldest (aspirin and ibuprofen [Motrin, etc.]) to the newest product still on the market (Celebrex [celecoxib]). There is virtually no evidence that **any** of the available NSAIDs or cox-2 inhibitors have greater analgesic efficacy overall than any other.⁷ Individual patients sometimes report that a particular product works better for them than others in the class; such inter-individual differences may be attributable to pharmacogenetic factors that are presently not understood, but most clinical trials do not favor any single drug over another. Despite the widespread impression that the cox-2 drugs were “super-aspirins” with greater analgesic or anti-inflammatory effects than older NSAIDs, this belief did not stand up to scrutiny in most clinical trials.⁷

For carefully selected patients with persistent chronic pain who are at particularly high risk of the gastrointestinal and cardiovascular complications of anti-inflammatory drugs, there is growing interest in the cautious use of opioids such as codeine, tramadol, or oxycodone.⁸

Gastrointestinal Adverse Events

NSAID-related complications in the upper gastrointestinal tract can range from dyspepsia to clinically evident ulcers and frank hemorrhage. At least four meta-analyses have been published on the topic, and all find a two- to five-fold increase in risk for such events among users of NSAIDs (range of odds ratios or relative risks from 2.7-5.4).^{9,10} These complications account for substantial morbidity and mortality; it was estimated that about 16,500 deaths and 107,000 hospitalizations are caused annually by NSAID-associated gastrointestinal toxicity.^{11,12}



NSAID-associated g.i. complications can affect anyone taking an NSAID or coxib, but several risk factors can identify the patients at highest risk of these problems^{10,13,14}: older age, history of gastrointestinal bleeding or peptic ulcer, and use of oral steroids or anticoagulants. Age appears to increase risk continuously above age 60.⁹

Strategies to minimize NSAID-associated gastrointestinal toxicity

Whenever possible, it makes sense to try and avoid use of NSAIDs in patients most likely to develop gastrointestinal toxicity. For high-risk patients who require NSAID therapy, one can add a proton pump inhibitor (PPI) or misoprostol. Use of a PPI has been clearly shown to reduce clinical gastrointestinal events in NSAID users.¹⁵ Several endoscopic studies also suggest that adding a PPI to an NSAID regimen can reduce gastrointestinal toxicity, as can use of ranitidine or misoprostol.¹⁵ All three strategies have been shown to reduce symptoms, with omeprazole-treated patients reporting the least dyspepsia. In one randomized trial, adding omeprazole to a conventional NSAID was as effective in reducing the risk of recurrent g.i. hemorrhage as treatment with celecoxib.¹⁵ In that study, patients with a prior NSAID-induced g.i. bleed were randomized to receive either celecoxib 200 mg b.i.d., or diclofenac 75 mg b.i.d. plus omeprazole 20 mg daily. No statistically significant differences in endoscopic ulcer rates were seen in the groups. These data suggest that prescribing an NSAID along with a proton pump inhibitor can provide gastroprotection equivalent to that of a coxib.

“Combining a conventional NSAID with a proton pump inhibitor was shown to provide about as much gastroprotection as use of a cox-2 inhibitor.”¹⁵

Misoprostol, a prostaglandin analogue, is another alternative to reduce the risk of NSAID-associated gastrointestinal bleeding.¹³ The MUCOSA trial enrolled almost 9,000 patients with rheumatoid arthritis who were taking NSAIDs; patients were then given misoprostol 200 mcg q.i.d. or placebo. After six months, 0.95% of those taking placebo had a serious gastrointestinal complication, compared with only 0.56% of patients receiving misoprostol ($p = 0.049$). However, overall more adverse events occurred in subjects taking misoprostol, including diarrhea (10%), abdominal pain (7%), dyspepsia (5%), nausea (5%), and flatulence (5%). Some recommend lower doses of misoprostol (200 mcg b.i.d.) to reduce side effects, although this dose has not been as thoroughly

tested. Because misoprostol can cause miscarriage or fetal anomalies, women of child-bearing age must have a negative pregnancy test before use.

Miscellaneous gastrointestinal toxicity

NSAIDs can cause ulcers anywhere along the g.i. tract, including the large intestine. Colitis has been also reported as a result of NSAID; these lesions may be confused with those of Crohn's disease. Liver toxicity is a rare complication of NSAID use. It may occur more frequently with diclofenac, but there is insufficient evidence on variations in the risk of hepatotoxicity by drug.¹⁶ Clinically important hepatotoxicity occurs in 1 per 10,000 patient courses of NSAIDs¹⁷; many more patients will have slight elevations in liver enzymes.

Cardiovascular Risks

Several possible mechanisms may explain the potential for coxibs (or older NSAIDs) to increase the risk of cardiovascular events. It was originally hoped that the selective inhibition of the cox-2 enzyme over cox-1 would provide pain relief and an anti-inflammatory effect without inhibiting the beneficial effects of cox-1, which included protection of the gastric mucosa. But it is now understood that inhibiting cox-2 may have unintended consequences as well, leading to thrombosis and vasoconstriction caused by an imbalance between thromboxane and prostacyclin; hypertension from inhibition of prostaglandin-dependent regulatory mechanisms; and oxidative stress. Each of these mechanisms, as well as a combination of them, has been suggested as a means of explaining the excess cardiovascular morbidity seen with use of these drugs.¹⁸

Evidence from randomized controlled trials

Rofecoxib (Vioxx): The potential for elevated thrombotic risk with rofecoxib was widely recognized at least as far back as 2000, with publication of the VIGOR trial.¹⁹ This study enrolled over eight thousand patients with rheumatoid arthritis and randomly allocated them to either 50mg daily of Vioxx or 500 mg b.i.d. daily of naproxen. Aspirin users were excluded. Patients given Vioxx had five times more myocardial infarctions, and the relative risk for severe thrombotic cardiovascular events was doubled. The event curves diverged after approximately six weeks.

The APPROVe (Adenomatous Polyp Prevention on Vioxx) trial was designed to determine whether Vioxx was effective against colon polyps, and tested the drug (25mg daily) against placebo for this indication. Patients given Vioxx had a 4-5 fold increase in the incidence of congestive heart failure; severe thrombotic cardiovascular events were about twice as frequent in the rofecoxib arm than in the placebo arm.¹ Other trials of Vioxx 25 mg did not demonstrate an increased cardiovascular risk, although these were generally of shorter duration.²⁰

Celecoxib [Celebrex]: The CLASS trial was designed to measure the gastroprotection afforded by Celebrex (400 mg b.i.d.) compared with ibuprofen 800 mg t.i.d. or diclofenac 75 mg b.i.d.²¹. Rates of cardiovascular events did not differ significantly between the Celebrex users and the combined NSAID user group. The Adenoma Prevention with Celecoxib (APC) trial, like APPROVe, was intended to determine whether a coxib could prevent the progression of colon polyps to adenoma. In that study, patients given high-dose (200 – 400 mg b.i.d.) long-term Celebrex doubled or tripled their rates of thrombotic cardiovascular events in a dose-dependent manner.² By contrast, however, the Prevention of Spontaneous Adenomatous Polyps (PreSAP) study, which also tested Celebrex versus placebo²² found no increase in cardiovascular events after 33 months in patients randomized to active drug (400 mg once per day) versus placebo.

Valdecoxib [Bextra]: Two controlled trials in patients undergoing coronary artery bypass grafting, CABG I²³ and CABG II³, found between 2.0 and 3.7 times the number of cardiovascular events in patients given Bextra and its intravenous formulation compared to placebo. Several other short-term studies of Bextra in patients with arthritis did not have adequate numbers of events to determine whether the medication increased cardiac risk.

The most consistent cardiovascular risk has been found with Vioxx; by contrast, naproxen may confer a slight cardioprotective effect.²⁴

Observational studies of cardiovascular risk

Several pharmacoepidemiologic analyses have examined rates of cardiovascular disease that occurred in typical patients taking coxibs or non-selective NSAIDs. Ray and colleagues studied users of Celebrex and Vioxx in a large state Medicaid program.²⁵ They found no increased risk with Celebrex, no



increased risk with 25 mg or less per day of Vioxx, but a doubling of the risk with Vioxx above 25 mg daily. Solomon and colleagues published a similar analysis using data from low-income Medicare beneficiaries who were also enrolled in drug benefit programs in Pennsylvania or New Jersey.²⁶ Users of coxibs were compared with non-users, as well as to each other and to users of older NSAIDs. The analysis found an increased risk of MI for Vioxx users, as compared to non-users and to Celebrex users. The latter drug was not associated with an increased risk of myocardial infarction in any of these analyses.

An FDA-sponsored epidemiologic analysis examined enrollees in a large health maintenance organization, comparing current use of coxibs and non-selective NSAIDs to remote past use (> 60 days prior) of these agents. A significant increase in cardiovascular risk was observed in patients taking Vioxx > 25 mg daily.²⁷ At lower dosages, the risk was also elevated but did not reach statistical significance. In that study, Celebrex was not associated with an increase in cardiovascular risk, and naproxen was associated with a slight increase in risk. Kimmel and colleagues conducted a case-control study in 36 hospitals²⁸ and found results consistent with other analyses. Two observational epidemiologic studies, from Ontario and Maryland, found no increased risk with any coxib.^{29,30} However, these studies have been criticized for evaluating non-representative patient populations, employing poorly defined inclusion criteria, and using flawed analytic models.

In many observational studies, use of naproxen has been found to be associated with a slight *reduction* in the risk of MI, but at a level far smaller than that seen with aspirin.²⁴

NSAID interactions with aspirin?

Clinical pharmacology studies have raised the possibility that some NSAIDs may block the cardioprotective effects of aspirin³¹ by interfering with aspirin's ability to inhibit platelet function. Some but not all clinical studies of this issue have also found an increased risk of cardiovascular events in patients concurrently taking aspirin and ibuprofen.³²⁻³⁴ Based on these findings, some recommend limiting use of ibuprofen in patients requiring cardioprotective aspirin.³⁵

Other Adverse Events

Renal

The nephrotoxicity potential of all NSAIDs and coxibs can lead to acute³⁶ and chronic renal dysfunction³⁷. Clinically, this may result in sodium retention, hyporeninemic hypoaldosteronism, pre-renal azotemia (which can progress to acute tubular necrosis if untreated), acute interstitial nephritis, and nephrotic syndrome.³⁸ Pre-renal azotemia is common in patients with diminished renal blood flow (especially the elderly), and probably results from inhibition of prostaglandin-mediated protection of renal circulation. It can be manifested clinically by edema, hypertension, and acute renal failure. Hyporeninemic hypoaldosteronism is of particular concern in diabetics using NSAIDs and can lead to hyperkalemia and a mild metabolic acidosis.³⁹

Cutaneous reactions

Almost every type of cutaneous drug reaction has been described with NSAIDs, including morbilliform eruptions, fixed drug eruptions, erythema multiforme (Stevens-Johnson syndrome or toxic epidermal necrolysis), pseudoporphyria, and photosensitivity. It has been estimated that over a quarter of all adverse drug reactions in the skin are caused by NSAIDs.⁴⁰ While most of these reactions are mild, the potentially fatal Stevens-Johnson syndrome has been particularly noted in patients taking valdecoxib (Bextra) and is one of the reasons that the Food and Drug Administration requested its manufacturer to remove it from the market.⁴¹

Central nervous system toxicity

Aseptic meningitis can occasionally occur in patients taking NSAIDs. Many cases have been in users of ibuprofen who had autoimmune disease, but this complication can also occur rarely in otherwise healthy patients taking other NSAIDs as well.⁴²

Patterns of Utilization and Economic Issues

One large population-based study found that among women 52 – 77 years of age, 27% reported using NSAIDs at least once a week, and 11% on ≥ 6 days per week.⁴³ There is considerable evidence that many coxib users do not have clear indications for preferential use of these drugs,^{44,45} with much coxib use driven by heavy marketing, physician preferences, specialty, and other non-clinical factors.^{44,46} At the same time, these studies also found that many patients given non-selective NSAIDs had risk factors for gastrointestinal toxicity.⁴⁷ Thus, there appeared to be both an over-use of coxibs and an under-use of strategies to reduce NSAID-associated gastrointestinal damage.

The coxibs can cost 5-10 times more than a generic NSAID, but do not confer greater benefit in most patients. In selected patients at high risk for gastrointestinal toxicity, they may be reasonably cost-effective: two analyses suggested that using coxibs in patients with at least one risk factor for an NSAID-associated gastrointestinal adverse event was economically reasonable.^{48,49} However, coxib use in young patients without risk factors was not at all cost-effective.

Clinical Recommendations

- For patients with arthritis, non-pharmacologic measures such as exercise, weight loss, taping, bracing, or cane use should be tried as an adjunct to drug treatment.⁴
- If medication is required, the American Heart Association recommends initial use of acetaminophen or aspirin before considering use of any NSAID.⁵⁰
- Acetaminophen, unless contraindicated, is first-line pharmacologic treatment for most patients, initially in the form of a two week trial of 1,000 mg t.i.d.-q.i.d.⁴
- If this is not sufficient, a trial of low-dose non-selective NSAID may be warranted. The available evidence suggests that naproxen appears to confer the least cardiovascular risk and may even reduce such risk, though any cardioprotective effect it may have is far smaller than that of aspirin.²⁴

- In all cases, it is important to use the lowest NSAID dose that will effectively control symptoms, and to keep the duration of use as short as possible to reduce risk.
- If a patient requires cardioprotective doses of aspirin, this should be given, but there is no evidence that this will eliminate the cardiac risks of NSAIDs or coxibs. Unfortunately, however, even low-dose aspirin appears to reduce or eliminate the gastroprotective effect that would have been conferred by a selective cox-2 inhibitor.²⁰
- Patients who will need NSAID treatment long-term can be risk-stratified based on the factors cited above. For patients with at least one of these factors, consider alternative strategies such as low potency opioids if no contraindications are present. For those who require an NSAID but have one or more risk factors for gastrointestinal toxicity, consider adding a proton pump inhibitor or misoprostol. Alternatively, celecoxib can be prescribed.
- All patients taking NSAIDs for more than a brief period should be monitored for gastrointestinal toxicity (dyspepsia, abdominal pain, fecal occult blood, black stools, anemia), development or exacerbation of hypertension, edema or congestive heart failure, and diminution in renal function.

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