

The COX-2 Report: the Good, the Bad, and the Unknown

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On 1 December 1998, a U.S. Food and Drug Administration (FDA) advisory panel voted to approve celecoxib (Celebrex), the first selective cyclooxygenase (COX)-2 inhibitor, for treating arthritis pain [1]. Rofecoxib (Vioxx) was approved several months later [2], and other selective COX-2 inhibitors are expected to be approved shortly. These drugs have been classified as nonsteroidal anti-inflammatory drugs (NSAIDs), which produce their therapeutic effects at least partially through inhibition of cyclooxygenase, the enzyme that makes prostaglandins. Research over the last decade has shown that there are at least 2 COX isoforms. COX-1 is constitutively produced; that is, it is present at low levels at all times and makes prostaglandins that are thought to protect the stomach lining from damage. COX-2, on the other hand, is expressed constitutively in the brain and the kidney but (importantly) not in the gut. COX-2 is also induced by inflammatory stimuli and produces prostaglandins that contribute to the pain and swelling of inflammation [3]. Selective COX-2 inhibitors have been in development for several years with the expectation that drugs that inhibit COX-2 and not COX-1 would be as efficacious as older NSAIDs but have lower gastrointestinal toxicity. Prelicensure studies to date support this presumption; however, definitive studies with important clinical endpoints are still in progress [1,2].

By its 7th week on the market, Celebrex had surpassed Viagra, the impotence medication, in generating record numbers of daily prescriptions early in its marketing [4]. Those who practiced medicine in the 1970s and 1980s may remember the mixture of dread and hope with which busy clinicians caring for patients with arthritis greeted the introduction of each new NSAID—dread about the spate of phone calls requesting the new drugs, each touted to be more effective and/or easier on the stomach, and hope that the new drugs would indeed deliver on this promise. If sales reports of the new COX-2 inhibitors are any indicator, there are a lot of phones ringing.

How should clinicians respond to patient requests for these new drugs? When should we replace old favorites with “new and improved” (but frequently more expensive)

alternatives? As in any therapeutic decision, in thinking about using COX-2 inhibitors in individual patients it is important to weigh known benefits and risks. In a decision involving new drugs or devices, it is also important to consider unknown risks. Thus, I classify my remarks into 3 categories: the good, the bad, and the unknown (which hopefully is not the ugly).

The Good

There is considerable but not definitive evidence that the best thing about the COX-2 inhibitors is the absence of the worst thing about older NSAIDs [1,2]. NSAIDs have dose-related, frequent, and serious upper gastrointestinal adverse effects, especially in elderly patients. These adverse effects include gastrointestinal symptoms, ulceration, hemorrhage, and death [5–14]. In a large study of elderly Medicaid enrollees, we found that NSAID users had an annual rate of ulcer hospitalization of 16 per 1000, a fourfold greater rate than that for nonusers of NSAIDs [6]. Data from this and other studies [5–10] suggested that among persons 65 years or older, 20% to 30% of all peptic ulcer hospitalizations and deaths were attributable to NSAID use. Among elderly NSAID users, nearly two thirds of ulcer-related hospitalizations and deaths were due to the NSAIDs. Thus, in the United States as many as 41,000 excess hospitalizations and 3300 deaths occur each year among elderly NSAID users [15]. A meta-analysis [16] of extant observational studies included NSAIDs most commonly in use in the 1980s. There were no important differences in the risk of serious upper gastrointestinal disease associated with these drugs except for ibuprofen, which conferred a lower risk than most other NSAIDs, likely due to the lower dosages used with this agent.

The gastrointestinal toxicity of NSAIDs has been at least partially responsible for a change in the therapeutic approach to patients with both rheumatoid arthritis and osteoarthritis. In the former, disease-modifying antirheumatic drugs

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(DMARDs) are instituted much earlier in the course of disease [17], and in the latter, acetaminophen is now frequently recommended as first-line therapy [18,19]. In addition, NSAID-associated toxicity has led to the development of and use of drugs as co-therapy to prevent complications. These drugs include misoprostol, a synthetic prostaglandin E₁ analogue [20]; proton pump inhibitors [21]; and high doses of histamine₂ (H₂)-receptor antagonists [22]. These drugs approximately halve the incidence of NSAID-associated ulcers but incur additional costs and cause their own adverse events. National estimates of NSAID utilization indicate a rapid rise in NSAID prescriptions from 1973 to 1983 and relatively stable numbers from 1984 through 1990. However, over the latter period there was a 46-fold increase in co-therapy with gastroprotective and/or antiulcer drugs [23].

One might also say that the best thing about older NSAIDs is part of the good thing about selective COX-2 inhibitors. Clinical trials suggest that despite the hoopla surrounding the introduction of each new NSAID, most NSAIDs introduced in the 1970s and 1980s have similar overall efficacy for treatment of arthritis [24]. However, having the choice of a number of different NSAIDs may be considered a bonus for patients, who seem to have considerable individual variation in response to these agents [25–27]. With all the publicity about the new COX-2 agents, it may be surprising to physicians and patients that the efficacy of these drugs is very similar to older NSAIDs. Indeed, given their mechanism of action, there is not good reason to believe that efficacy would be superior. Since NSAIDs rarely cause patients with arthritis to become asymptomatic, the efficacy of these drugs for most patients must be considered modest but important. The rapidity with which patients switch to newly marketed NSAIDs attests to this modest efficacy as well as to the power of advertising. For some patients, specific NSAIDs will have remarkable efficacy. Thus, the availability of another choice offers patients another chance at a better result.

The Bad

There is a poor connection between NSAID-associated gastrointestinal symptoms and the development of serious upper gastrointestinal toxicity [28,29]. Singh et al [28] found that 81% of patients with serious NSAID-associated complications reported no prior dyspepsia. Laszlo et al [29] reported that 40% of patients with a first episode of NSAID-associated upper gastrointestinal bleed had no warning symptoms at all. Despite the poor correlation between “dyspepsia” and serious ulcer disease, these symptoms often result in diagnostic or therapeutic interventions. The most common adverse effects reported with celecoxib [1] and rofecoxib [2] have been abdominal pain, diarrhea, and dyspepsia. Thus, even if the COX-2 inhibitors do not cause serious gastrointestinal toxicity, they still may be associated with increased

use of diagnostic maneuvers or drugs to treat dyspepsia. Older NSAIDs have been associated with a doubling of the use of H₂-receptor blockers. In fact, in 1 study, these agents accounted for approximately 43% of the excess cost incurred by NSAID-associated adverse effects among regular NSAID users aged 65 years and older [30]. These results predated widespread use of misoprostol and proton pump inhibitors, so it is likely that excess costs due to agents used for treatment of gastrointestinal symptoms or prophylaxis against serious gastrointestinal events has increased. It is unknown how often users of COX-2 inhibitors will be prescribed these types of co-therapy. However, co-therapy will be an important consideration when comparing the total costs of COX-2 inhibitors (drug costs plus costs of adverse effects) with the costs of older NSAIDs.

NSAIDs have other adverse effects unrelated to the gastrointestinal tract, including nephrotoxicity [31–37] and hepatotoxicity [38]. Particularly worrisome is the ability of NSAIDs to increase blood pressure, a fact that has been underappreciated clinically. As summarized recently by Whelton [39], even small increases in blood pressure can have a major impact on health: a 5– to 6–mm Hg increase in diastolic blood pressure for several years increased cerebrovascular accidents by 67% and coronary artery disease by 15%. Similar declines in blood pressure have been associated with a 35% to 40% reduction in stroke and a 20% to 25% reduction in congestive heart failure. Numerous studies summarized in 2 large meta-analyses [40,41] provide convincing evidence of NSAIDs' deleterious effects on blood pressure, particularly among those already being treated for hypertension. Gurwitz et al [42] documented a twofold increase in use of antihypertensives among NSAID users compared with controls. Given the prevalence of hypertension in the United States and the high stakes associated with small increases in blood pressure, the public health implications of chronic NSAID use in elderly, at-risk populations are potentially enormous. This surely represents another frontier for the next generation of NSAIDs. To date, there is no evidence that renal effects of the COX-2 inhibitors are different from the effects of older NSAIDs. Thus, blood pressure elevation and edema will be relatively common due to COX-2 inhibition in the kidney. Clinically important acute renal failure due to these drugs will likely be relatively rare, as with other NSAIDs. However, renal failure remains an important consideration for patients with pre-existing renal insufficiency or other conditions (eg, heart failure, cirrhosis) that may compromise effective renal blood flow.

The cost to the pharmacist for 30 days' treatment with either of the approved COX-2 inhibitors ranges from \$73 to \$86, similar to the more expensive nongeneric NSAIDs but 10 to 30 times higher than generic-brand ibuprofen and naproxen [1,2]. However, other cost considerations include

treatment for adverse effects as well as for prophylaxis. In a study of clinical practice in 1989, we estimated that on average, a regular NSAID user incurred \$110 in excess costs annually due to adverse effects: 49% due to hospitalizations for ulcers and bleeding, 43% due to gastrointestinal drugs used for both treatment and prophylaxis, and 7% due to outpatient procedures. These costs are likely to have changed with wider use of co-therapy that is both more expensive and effective in preventing complicated ulcers.

The Unknown

Numbers of patients enrolled in clinical trials of COX-2 inhibitors measure in the thousands, yet there are millions of persons in the United States taking NSAIDs who are potential users of these new drugs. Should all of them switch today? Previous experience suggests that the rapid uptake of new drugs may result in a distressingly large number of persons exposed to rare, unanticipated side effects. The NSAID zomepirac was first marketed in the United States in 1980 for both acute and chronic pain. Shortly thereafter, zomepirac-associated anaphylaxis was reported. After intense publicity surrounding this unusual, possibly idiosyncratic, and occasionally fatal NSAID-associated reaction, the drug was permanently withdrawn by the manufacturer in 1983 [43]. Within 4 months of its introduction, zomepirac accounted for 11% of new analgesic prescriptions in the United States. This has been a common pattern with new NSAIDs. In many instances in which a serious adverse event resulted in drug withdrawal, an unusually high reporting rate of the adverse event was observed within the 1st year of marketing [44]. Similarly, benoxaprofen was available for about 2 years in Great Britain before it was withdrawn because of severe hepatotoxicity in elderly persons, presumably due to its very long half-life [45]. The typically rapid uptake of new NSAIDs is currently being repeated with the new COX-2 inhibitors. One needs to question whether this is rational drug use. For patients who are not at high risk for serious adverse events secondary to NSAIDs, waiting for at least 1 to 2 years of postlicensure experience before switching to these new agents seems prudent.

The beneficial vascular effects of low-dose aspirin are mediated through a COX-1 effect on platelets. Some but not all NSAIDs have a platelet effect, but vascular benefits of non-aspirin NSAIDs have not been demonstrated. Since this is a COX-1 effect, the COX-2 agents would not be expected to have this benefit [46]. Aspirin also inhibits prostacyclin release from endothelial cells, a dose-dependent thrombogenic effect that is outweighed by the antiplatelet effect. There has been some concern about prothrombotic effects of NSAIDs with the much greater selectivity of COX-2 compared with COX-1, but there are few data to address this concern.

Unknowns are not always ugly [47]. Recent data suggest that NSAIDs may also confer some unexpected benefits.

Aspirin and nonaspirin NSAIDs have been convincingly associated with about a 30% reduction in colon polyps, colon cancer, and death from both colon cancer and selected other upper gastrointestinal cancers. Clinical trials are ongoing to determine whether these results from multiple observational studies can be replicated in practice. COX-2 inhibitors would be expected to have a similar effect on gastrointestinal cancers, but data from clinical studies are lacking. There is also evidence that NSAIDs may prevent and/or slow the progression of Alzheimer's-type dementia. Again, confirmatory studies are ongoing.

The Bottom Line

If COX-2 inhibitors fulfill their promise of being equally efficacious with minimal serious gastrointestinal toxicity and no increase in other adverse events, they will eventually supplant older NSAIDs for most situations, including chronic arthritis. Older NSAIDs will likely remain in use for certain patients who seem to respond better to particular drugs and have a low risk of serious gastrointestinal toxicity. Some of these drugs will likely disappear or will be used infrequently, much like phenylbutazone is today. That these changes have not yet occurred is primarily because of unknown factors related to COX-2 inhibitors and their relatively high cost. Experience with new drugs in general and with NSAIDs in particular suggest that, for most patients not at high risk for NSAID-associated adverse effects, waiting 1 to 2 years before using the new drugs is a reasonable strategy.

What about patients with high-risk conditions? Persons at high risk for serious NSAID-associated gastrointestinal toxicity include those with advanced age, history of ulcer or upper gastrointestinal bleeding, concomitant use of corticosteroids or anticoagulants, serious comorbidities, or those on high doses of NSAIDs [48]. For these patients, co-therapy with misoprostol, a high-dose H₂-receptor antagonist, or a proton pump inhibitor or therapy with a selective COX-2 inhibitor are reasonable options. Ultimately, choice of therapy must be a joint decision between patients and their physicians. Misoprostol is the only drug that is FDA-approved for prophylaxis against NSAID-related adverse gastrointestinal events. However, recent research suggests that high-dose H₂-receptor antagonists and proton pump inhibitors may offer similar protection with fewer side effects. COX-2 inhibitors are attractive from a convenience standpoint (1 drug instead of 2); however, more studies with larger numbers of patients are needed to better define their safety profile. In addition, it may be that, as with older NSAIDs, these drugs will be associated with a high use of H₂-blockers and proton pump inhibitors to control symptoms rather than for prophylaxis.

If and when COX-2 inhibitors replace older NSAIDs for most clinical indications, it will remain important to consider their risks and benefits versus acetaminophen. The ability

of standard NSAIDs and COX-2 inhibitors to cause or exacerbate hypertension is a serious consideration. Primary care physicians need to educate their patients about nonpharmacologic adjuncts to therapy including arthritis self-help education, joint protection efforts, and reasonable exercise regimens. More research is needed on developing safe regimens with minimal adverse effects for those with chronic symptoms, including evaluation of "as-needed" versus long-term medical therapy, combined use of acetaminophen and low-dose NSAIDs versus higher NSAID doses, and use of other modalities including topical, intra-articular, and nonpharmacologic therapies.

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