

With the withdrawal of COX-2 inhibitors, opioids are an obvious alternative choice for pain

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INTRODUCTION

Opioids are often used in combination with other analgesics in multimodal approach. Pharmacotherapy in alleviating pain may require, in addition to an opioid, nonsteroidal anti-inflammatory agents. This article will help the clinician determine when to use nonsteroidal anti-inflammatory agents and which nonsteroidal anti-inflammatory agents may be better options to use in conjunction with opioid management.

The cyclooxygenase 2 (COX-2) selective nonsteroidal anti-inflammatory drug (NSAID) rofecoxib (Vioxx[®]) was voluntarily removed from the worldwide market in September 2004. Its manufacturer (Merck) announced that the decision was based on new data from a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial called APPROVe (Adenomatous Polyp Prevention on Vioxx). The APPROVe trial revealed a twofold increase in the risk of developing cardiovascular (CV) embolic events, such as stroke and myocardial infarction, in patients receiving rofecoxib 25 mg daily for 18 months or more.¹ More recently, the news of a CV signal with celecoxib (Celebrex[®], Pfizer) has raised concerns that the problem of an increased CV risk may be a class effect shared by all the selective COX-2 inhibitors.

In light of these apparent risks to patients, physicians and other practitioners should become familiar with the mechanisms of NSAID action, the differences among COX-2 selective NSAIDs, and alternative NSAID options.

BACKGROUND

The US Food and Drug Administration's (FDA) approval of rofecoxib and celecoxib (Celebrex) in 1999 led to a steady surge in the use of COX-2 selective drugs for inflammatory-mediated pain. Another COX-2 selective NSAID, valdecoxib (Bextra[®]), was released in November 2001, and others are currently under investigation. Lower gastrointestinal (GI) toxicity and no effect on bleeding time were cited as the advantages of these drugs over the nonselective NSAIDs such as ibuprofen (Advil[®], Motrin[®])

and naproxen (Aleve[®], Naprosyn[®]). These characteristics are important considerations, particularly in surgical patients and individuals receiving long-term NSAID therapy for chronic pain. Direct-to-consumer advertising fueled a rapid rise in the use of COX-2 selective NSAIDs. Television advertising budgets for COX-2 selective agents skyrocketed over the last five years, and these analgesics rapidly dominated the prescription NSAID market. It was estimated that 80 million individuals had taken rofecoxib by the time it was withdrawn in September 2004.² Pfizer agreed in December to an FDA request to suspend all direct-to-consumer marketing of Celebrex after the news of a CV signal.

An increased risk of CV events was first seen in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.³ As a result of this study, the FDA adopted labeling changes for rofecoxib in April 2002 that included information about the increased risk of CV events compared with naproxen. Originally, the difference in CV risk was attributed to a cardioprotective effect of naproxen—which was later proven to be false⁴—rather than specifically to rofecoxib. This cardioprotective interpretation was reiterated in a 2001 meta-analysis of randomized trials of rofecoxib and three meta-analyses of naproxen and myocardial infarction published in 2002.⁵ However, in August 2004, the FDA initiated and funded a retrospective database analysis that showed that rofecoxib, when taken at more than 25 mg per day, was associated with a greater risk of acute myocardial infarction and sudden cardiac death than other NSAIDs such as Celebrex.⁴ This increased risk led Merck to voluntarily withdraw rofecoxib.

MECHANISMS OF NSAID ACTION

The COX enzyme is crucial to the formation of prostaglandins and exists in two isoforms: a constitutive (i.e., always present) isoform called COX-1, and an inducible isoform called COX-2 that is expressed at inflammation sites. The COX-2 selective NSAIDs (rofecoxib, celecoxib, valdecoxib) selectively inhibit COX-2 and thereby inhibit prostaglandin E₂ (PGE₂). Inhibition of

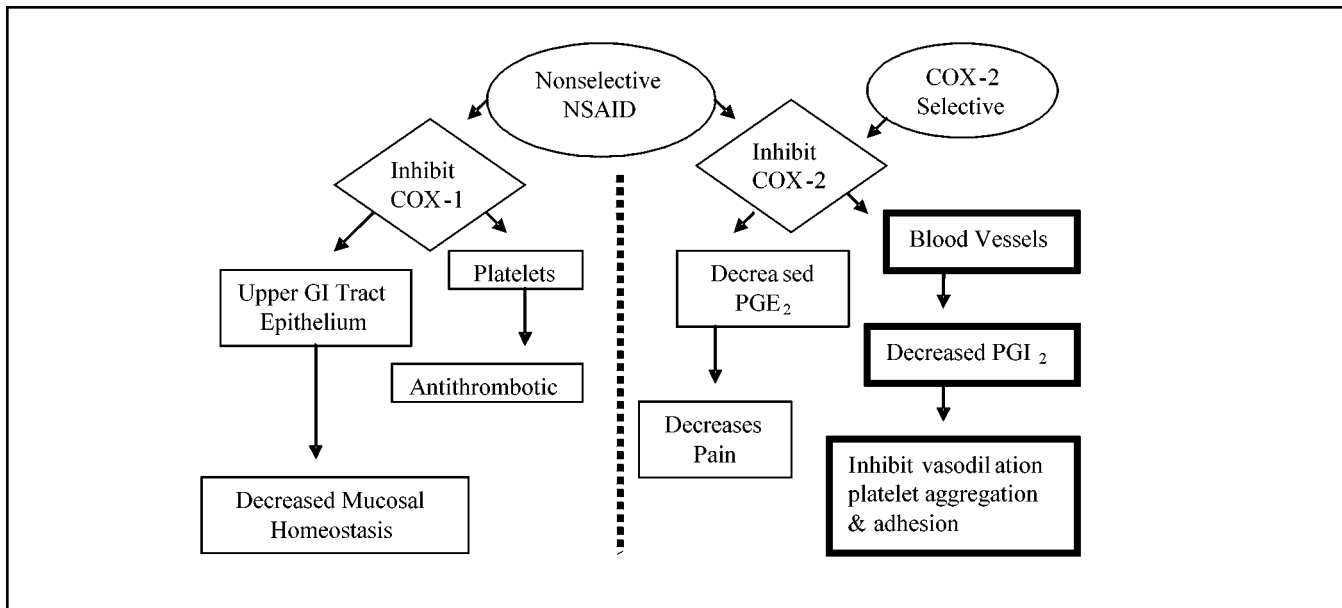


Figure 1. Schematic pathways of some of the functional effects of inhibition of COX-1 and COX-2. Copyright 2004 by Sarah E. Hutchison. Used with permission.

PGE₂ results in a decrease in inflammatory-mediated pain (Figure 1). However, the COX-2 selective NSAIDs also inhibit prostaglandin I₂ (PGI₂), another type of prostaglandin found in blood vessels, which is a vasodilator.⁶ The decrease in PGI₂ in the blood vessel diminishes vasodilation and promotes platelet aggregation and adhesion.⁷ This is thought to be, at least in part, the mechanism for the increased CV events observed in the patients who took rofecoxib.

Nonselective NSAIDs, such as aspirin, ibuprofen, naproxen, and ketorolac (Toradol®), inhibit both COX-1 and COX-2. This inhibition produces both a decrease in inflammatory-mediated pain and an antithrombotic effect on platelets.

DIFFERENCES AMONG THE COX-2 SELECTIVE NSAIDS

The reason why rofecoxib has been associated with a higher risk for CV events compared to other drugs in its

class is still under investigation. It may lie in the differences in duration of effect or degree of COX-2 selectivity among the various NSAIDs. A drug's duration of effect can be predicted by its half-life (i.e., the time it takes for the amount of drug in the body to be reduced by 50 percent). Figure 2 demonstrates that rofecoxib has a longer duration of effect (half-life of 17 hours), and Figure 3 shows that both rofecoxib and valdecoxib have a higher degree of COX-2 selectivity compared to other NSAIDs. Aspirin has much more selectivity for the COX-1 and a very long effect on platelet inhibition (antithrombotic effect).

ALTERNATIVE NSAID OPTIONS

There are many pain-relieving alternatives to rofecoxib (Table 1) for people who suffer from inflammatory-mediated pain (e.g., arthritis). It's important for the healthcare professional to conduct a complete evaluation

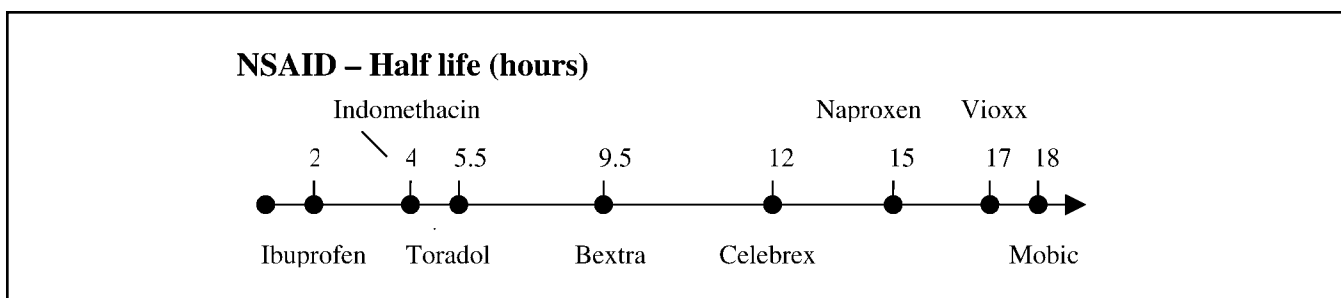


Figure 2. NSAID—half life (hours). Note: Duration of effect is dependent on individual hepatic metabolism and renal function and may vary. Copyright 2004 by Rob Hutchison. Used with permission.

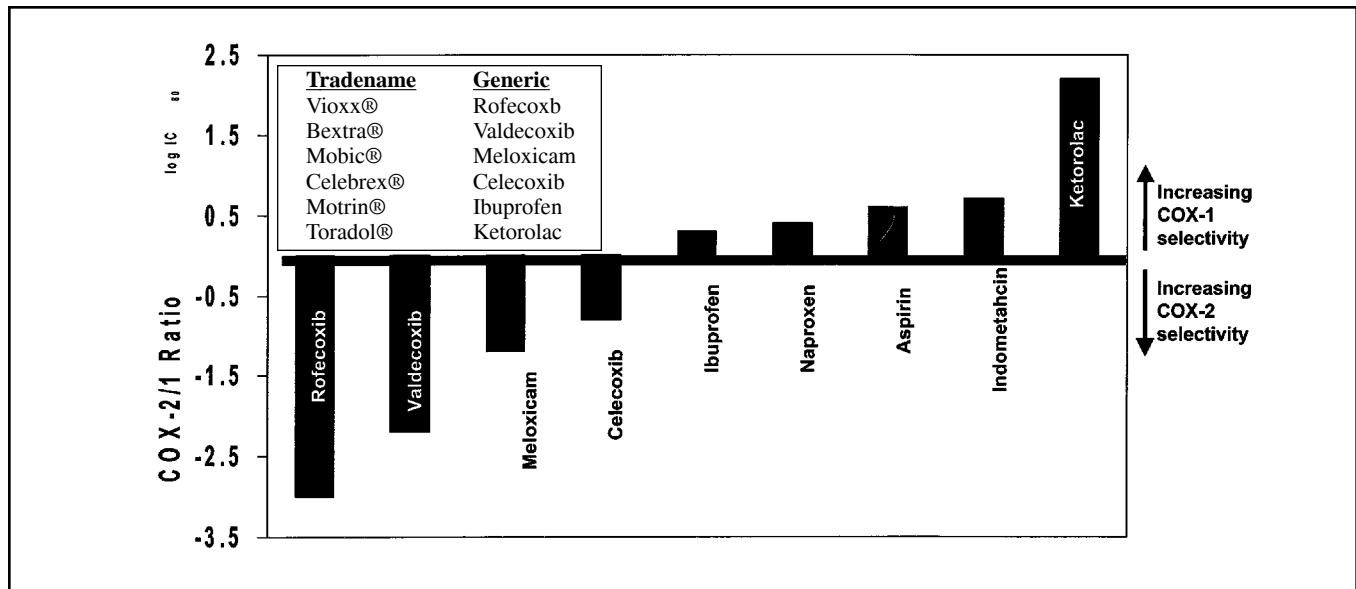


Figure 3. COX-2 selectivity. Adapted from Warner TD, Mitchell JA: Cyclooxygenase: New forms, new inhibitors, and lessons from the clinic. *FASEB J.* 2004; 18(7): 790-804.

of the patient’s risk factors when considering the use of an NSAID, particularly when long-term treatment is anticipated.

At this time, the FDA has issued an advisory statement to not use nonselective NSAIDs longer than 10 days without physician consultation. The advisory statement also cautioned use of COX-2 selective agents in high-risk settings (immediately after heart surgery).⁴ Valdecoxib (Bextra), as reported by Pfizer Inc., has undergone a label change to warn about an increased risk of CV events (about 1 percent of patients) immediately following coronary artery bypass graft surgery—a very specific medical setting.⁸ Other NSAID options with a low GI adverse-effect profile include the nonaspirin salsalate products, such as salsalate (Disalcid®). The nonselective

NSAIDs, such as ibuprofen, are appropriate for individuals with adequate renal function and no GI or CV risk factors for short-term use (< 10 days).⁴

It’s important to remember that aspirin appears to eliminate any GI protection offered by a COX-2 selective NSAID. Therefore, using a COX-2 selective agent while taking aspirin as an analgesic may not be cost-effective. However, be sure to remind individuals not to discontinue their cardioprotective aspirin when taking a COX-2 selective NSAID.

A patient’s renal function and the existence of underlying hypertension are other considerations when selecting an NSAID. Studies are lacking on the safe use of NSAIDs in individuals with renal disease. The COX-2 selective NSAIDs offer no additional renal protection

Table 1. COX-2 selective considerations

Risk	May consider COX-2	Avoid Cox-2*
Less ↓ More	Short-term use; risk for GI bleed	Daily aspirin use ¹⁰
	No cardiovascular disease (CVD)	Risk factors for CVD ¹¹
	Long-term use; risk for GI bleed	Long-term use; CVD
	Renal impairment (RI), 3 to 7-day use	Long-term use; RI and CVD

* More studies are needed to determine safety. FDA Public Health Advisory, December 23, 2004.⁴

compared with the nonselective NSAIDs. Short-term NSAID use for precise indications, such as a three- to seven-day treatment of painful gout, may be appropriate in patients with end-stage renal disease.⁹

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