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After Vioxx: The Issue of Safety in Prescribing COX-2 Inhibitors

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After the voluntary withdrawal of Vioxx (rofecoxib) from the market in September 2004 following reports of increased cardiovascular events associated with the drug, there was a call from some quarters for a similar action for all selective COX-2 inhibitors (coxibs). Traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) always have been troubled by a significant risk of serious gastrointestinal complications resulting in substantial morbidity and mortality. The discovery of two isomers of cyclooxygenase (COX-1 and COX-2) in the 1990s led to the development of the coxibs, with their ability to selectively inhibit the inflammatory effects of COX-2 while preserving the beneficial effects of COX-1 on the gastrointestinal tract.

Selective COX-2 inhibition, however, may block the ability of the vascular endothelial cell to protect itself against platelet adhesion while allowing COX-1 mediated platelet adhesion to proceed, tilting the balance of hemostasis toward thrombosis.

As they are faced with concerned patients and the need to make decisions regarding appropriate use of anti-inflammatory drugs, clinicians will benefit if they are aware of the events that led to the withdrawal of rofecoxib from the market. They also need to understand the unique properties of the coxibs and how they may impact on the cardiovascular system and on the concept of a coxib class effect. This article reviews the current clinical knowledge regarding the coxibs and their cardiovascular effects. Recommendations for prescribing anti-inflammatory drugs in common clinical situations are provided.

—The Editor

Introduction

On September 30, 2004 Vioxx (rofecoxib) was voluntarily withdrawn from the worldwide market by Merck and Co. due to a reported increase in cardiovascular events associated with the drug.[1]

A selective COX-2 inhibitor of prostaglandin production, rofecoxib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of osteoarthritis, rheumatoid arthritis, severe menstrual cramps, acute pain, and juvenile rheumatoid arthritis. It accounted for $2.5 billion in worldwide sales in 2003, and was used by 20 million people at the time of its recall.[2]

This article will review the events leading to the withdrawal of rofecoxib from the market, describe the unique properties of selective COX-2 inhibitors (also known as coxibs) that may impact the cardiovascular system, and explore the concept of a

class effect that could influence clinical decisions regarding available coxibs. This review will conclude with recommendations for prescribing anti-inflammatory drugs in common clinic situations.

The Rofecoxib Story

NSAIDS commonly have been used for many years to treat arthritis, menstrual pain, and other acute and chronic painful conditions. Their use has been limited by dyspepsia and gastric or duodenal ulcers leading to perforation, obstruction, and serious gastrointestinal bleeding. NSAID gastropathy was estimated to cause 16,500 deaths annually in patients with osteoarthritis or rheumatoid arthritis in the United States.[3] The discovery in the early 1990s of two isomers of the cyclooxygenase enzyme that catalyzes transformation of arachadonic acid to prostaglandins and thromboxanes led to the development of the coxibs.[4]

In 1999 the FDA approved rofecoxib for treatment of acute pain, dysmenorrhea, and osteoarthritis. This approval was based on phase III clinical trials involving approximately 5000 patients that did not anticipate or assess for an increased cardiovascular risk. In 2000 the Vioxx Gastrointestinal Outcomes Research study (VIGOR)[5] was published. This randomized, double-blind study of 8076 patients with rheumatoid arthritis compared the occurrence of gastrointestinal toxicity of rofecoxib 50 mg/day to naproxen (Aleve, Anaprox, Naprosyn) 1000 mg/d. Median study duration was 9 months, and aspirin use was not allowed. The primary conclusion of the study was that treatment with rofecoxib was associated with 60% fewer clinically important upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers) than treatment with naproxen. It also confirmed that both drugs had similar efficacy in the treatment of rheumatoid arthritis. It is important to note that investigators chose a high (50 mg/day) dose of rofecoxib for this study. The good news was that even this high dose of the drug was associated with a reduced incidence of upper gastrointestinal events compared with naproxen.

An unexpected finding of the VIGOR trial[5] was an increased rate of acute myocardial infarction (AMI) in the rofecoxib group compared to the naproxen group (0.4% vs. 0.1%). Although aspirin use was not allowed, 4% of the patients met FDA criteria for the use of aspirin for secondary cardiovascular prophylaxis. These patients accounted for a disproportionately large 38% of the patients who had AMI. The investigators theorized that this effect could be due to a coronary protective effect of naproxen, based on its ability to inhibit platelet aggregation.[5] Other possibilities included a random event or a deleterious effect of rofecoxib.

An FDA advisory committee met in February 2001 to review results of the VIGOR study. The committee determined that, based on current data, the risk/benefit ratio still was sufficiently favorable but recommended changes in labeling and additional studies of cardiovascular risk. The new labeling advised caution in prescribing rofecoxib to patients with ischemic heart disease and stated that the 50 mg dose should not be used for more than five days.

Three large prospective, randomized, placebo-controlled trials of rofecoxib already had been initiated in 2000. These included the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial and the Vioxx in Colorectal Therapy, Definition of Optimal Regimen (VICTOR) study. A third study for prostate cancer had begun. These studies were structured to include the incidence of cardiovascular outcomes as a prespecified secondary end point.

Three studies[6-8] concluded that naproxen exerted a cardiovascular protective effect. This supported the hypothesis put forth in the VIGOR study that the reason more patients taking rofecoxib had AMI than those taking naproxen was that naproxen decreased the incidence of myocardial infarction. Other studies, however, failed to show a cardioprotective benefit of naproxen or other NSAIDs.[9,10]

Two other retrospective cohort studies found an increased cardiovascular risk associated with doses of rofecoxib higher than 25 mg daily.[11,12]

Recently a nested case control study was performed by the FDA in collaboration with Kaiser Permanente, California to evaluate the relative frequency of cardiovascular events in approximately 1.4 million patients receiving a variety of NSAIDs.[13] After adjusting outcomes for other cardiovascular risk factors, the risk for serious coronary heart disease associated with rofecoxib 25 mg/day was increased 1.29 relative to

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Figure 1. Synthesis, Function, and Inhibition of COX 1 and 2

	COX 1	COX 2
Enzyme synthesis	Constitutive	Only after induction (IL-1, TNF-alpha, lipopolysaccharide)
Function	Physiologic protection of the stomach, regulation of platelet aggregation (TXA_2), peripheral vascular resistance (PGI_2, PGE_2), sodium excretion (PGE_2)	Proinflammatory prostanoids (PGE_2, PGI_2 and TXA_2) in fibroblasts and macrophages and other cells
Inhibition by NSAIDs	COX 1 ← Relative effect favors → COX 2 Indomethacin Aspirin Piroxicam Ibuprofen Diclofenac Meloxicam Celecoxib Rofecoxib	

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remote NSAID use, and the relative risk of doses higher than 25 mg/day was 3.15 compared to controls. Naproxen use also was associated with an increased cardiovascular risk of 1.18, a finding not supportive of a cardioprotective property of the drug.

On the heels of the FDA-Kaiser Permanente study came the premature cessation of the APPROVe[1] study by the data safety and monitoring board due to a significant increase in cardiovascular risk associated with rofecoxib. APPROVe was a randomized, placebo-controlled, double-blind study initiated in 2000 to evaluate the efficacy of rofecoxib 25 mg/day in reducing recurrence of neoplastic colon polyps in patients with colon cancer. This long-term trial did not identify any early issues; however, by 18 months there was a two-fold increased risk of confirmed cardiovascular events, including myocardial infarction and stroke, associated with rofecoxib. As a result of this outcome, Merck & Co. withdrew rofecoxib from the world-wide market on Sept. 30, 2004.

The Unique Properties of the Coxibs

NSAIDs exert their major effects through inhibition of cyclooxygenase, the enzyme that converts cell membrane arachadonic acid into prostaglandins and thromboxanes.[4,14] Cyclooxygenase exists in two forms, COX-1 and COX-2. These two isomers are present in different cells in the body and are activated under different circumstances leading to different physiologic and pathologic effects. (*See Figure 1.*) COX-1 is constitutively expressed (regularly produced) in all cells, thus it is sometimes referred to as a "housekeeping" enzyme. Gastric mucosal-protective prostaglandin E2 is COX-1-derived, as is platelet aggregation-enhancing thromboxane A_2 (TXA_2). COX-2 is found only in certain cells such as inflammatory and endothelial cells, and its production is induced by inflammatory or mitogenic stimuli. These distinctions are not absolute; COX-1 is inducible in some situations, and COX-2 can be constitutively expressed in some tissues such as the kidney or brain.[14] Traditional (nonselective) NSAIDs such as indomethacin (Indocin) and naproxen inhibit the activity of both isomers of cyclooxygenase. The newly developed coxibs (also known as COX-2 selective or COX-1 sparing inhibitors) include celecoxib (Celebrex), rofecoxib, and valdecoxib (Bextra). Etoricoxib is available in Europe, and lumiracoxib is being evaluated for approval by the FDA. The development of the COX-2 inhibitors was based on the premise that they might suppress undesirable COX-2 mediated inflammation while sparing desirable COX-1 protective functions related to gastric mucosa. The VIGOR trial was a resounding success in this regard. Rofecoxib was as effective as naproxen in treating patients with rheumatoid arthritis, yet was associated with substantially fewer major gastrointestinal complications.[5]

Undesirable vascular thrombosis is a potential downside of unopposed COX-2 inhibition. Platelet-derived TXA_2 promotes platelet adhesion, vasoconstriction, and vascular proliferation.[1,4,10] Low-dose aspirin exerts its protective effect largely by blocking platelet COX-1-induced TXA_2 production. (*See Figure 2.*) The irreversible acetylation of the platelet COX-1 receptor allows aspirin to exert its effect for the life of the platelet, long after the drug has disappeared from the blood. Aspirin reduces vascular events by approximately 30%.[15] Prostaglandin I_2 (PGI_2), which is produced by vascular endothelial cell COX-2, counters thrombosis by inhibiting platelet adhesion, vascular proliferation, and by promoting vasodilatation.[1] Non-selective NSAIDs inhibit both platelet TXA_2 production and endothelial cell PGI_2 production. (*See Figure 3.*) Coxibs have pharmacological actions almost

Figure 2. Low Dose Aspirin Platelet-Endothelial Cell Effects

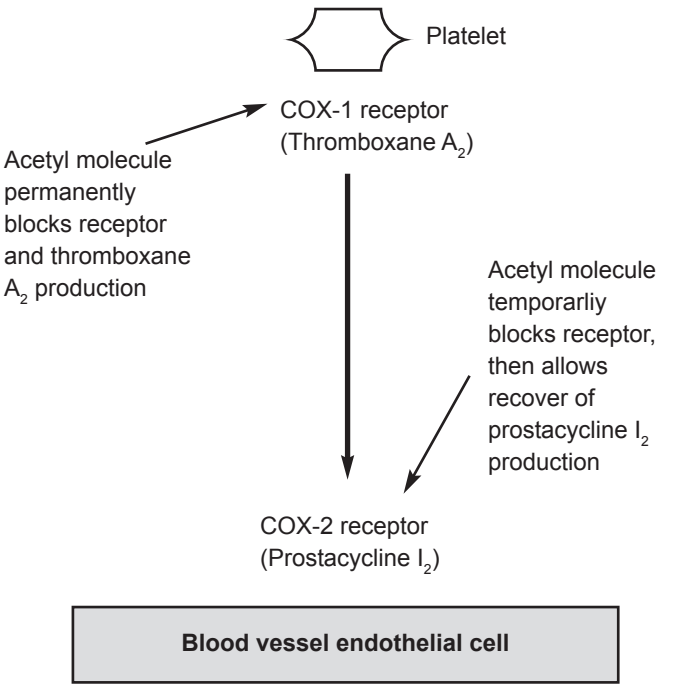
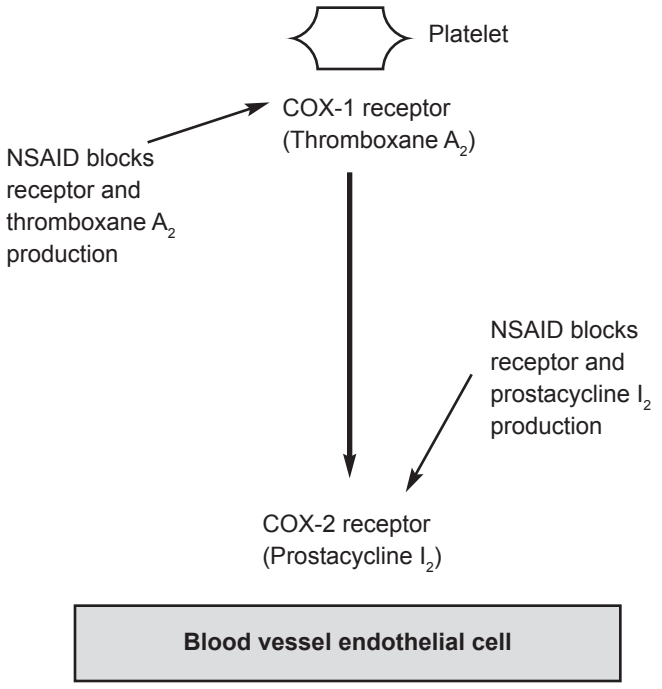


Figure 3. Non-selective NSAID Platelet-Endothelial Cell Effects



diametrically opposite to those of aspirin. (*See Figure 4.*) By selectively inhibiting COX-2-mediated PGI_2 production, coxibs may block endothelial cell protection against platelet adhesion and vasoconstriction, leading to an undesirable tendency toward vascular thrombosis. This effect appears to be more pronounced in patients who are already at risk for cardiovascular events. Only 4% of the VIGOR study patients met FDA indications for secondary cardiovascular prophylaxis, yet these patients accounted for 38% of myocardial infarctions observed in the study.[5] Increasing vascular laminar shear stress, as would be expected to occur in atherosclerotic lesions, stimulates endothelial cell expression of COX-2 (thus PGI_2 formation) presumably as a protective action.[1,14,16] By blocking this response to injury, coxibs could increase risk particularly in patients predisposed to cardiovascular disease. It is important to emphasize, however, that PGI_2 is only one of several endothelial-derived substances that oppose platelet adhesion. Nitric oxide, CD39/ecto-ADP-ase, and platelet endothelial cell adhesion molecule all serve to counter platelet adhesion and aggregation and counteract thrombosis.[14]

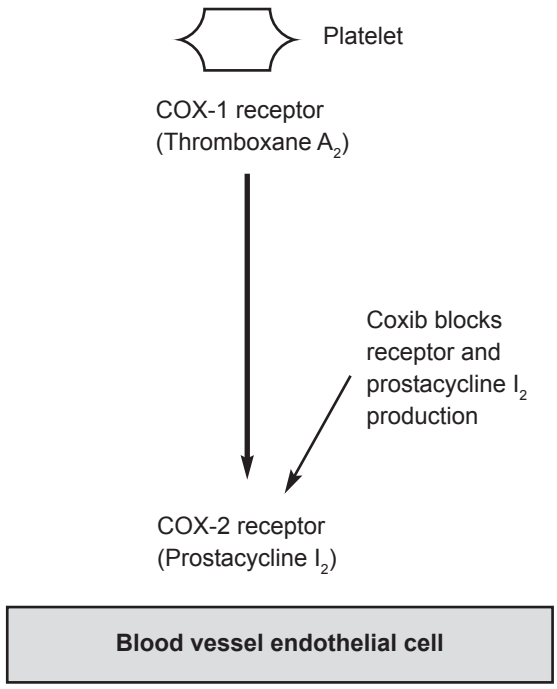
NSAID Effects on Blood Pressure

Sustained increases in blood pressure are associated with AMI and stroke. Both nonselective as well as COX-2 selective NSAIDs raise blood pressure through renal prostaglandin blockade.[4] This effect most often is seen in hypertensive patients receiving angiotensin-converting enzyme inhibitors, beta-blockers, or loop diuretics.[17,18] In the VIGOR study, rofecoxib 50 mg/day was associated with a 3.6 mm increase in systolic blood pressure compared to naproxen 1000 mg/day.[5] In a study of older hypertensive patients with osteoarthritis, valdecoxib 25 mg/day was associated with a mean rise in systolic pressure of 2.6 mmHg compared with -.05 mmHg for celecoxib 200 mg/day.[17] Edema was experienced by 9.5% of rofecoxib but only 4.9% of celecoxib-treated patients. Two other studies of rofecoxib and celecoxib in older hypertensive patients produced similar findings, suggesting that all coxibs are not alike.[19,20]

NSAIDs, Inflammation, and Atherosclerosis

Alternatively, NSAIDs theoretically could reduce atherogenesis by their anti-inflammatory actions. There are several lines of evidence suggesting that systemic inflammation may play a role in promoting atherosclerotic disease.[21-26] This is true of both chronic inflammation and acute inflammatory processes that are associated with a transient increased risk of AMI.[24] High levels of C-reactive protein, a marker of systemic inflammation, are associated with an increased risk of coronary artery disease.[23] Two systemic diseases, rheumatoid arthritis and systemic lupus erythematosus, are independent risk factors for AMI.[26] NSAIDs, by virtue of their anti-inflammatory effects, could reduce systemic inflammation and reduce risk of acute or chronic atherosclerotic disease. This idea is supported by a recent intriguing study reporting, in chronic nonselective NSAID users, an almost three-fold increase in myocardial infarction within one month of discontinuation of the drug.[25] The authors also offered other theories, such as a vascular tissue inflammatory rebound effect or acti-

Figure 4. Coxib Platelet-Endothelial Cell Effects



vated platelet aggregation after termination of cyclooxygenase mediated inhibition of thromboxane. Regardless of cause, this study suggested that there may be a vulnerable period for AMI after discontinuation of nonselective NSAID use.[25]

Is There a Coxib Class Effect?

The removal of rofecoxib from the market has heightened concern regarding use of all coxibs and has led some critics to claim that the burden of proof of safety now lies with the FDA and the manufacturers of coxibs.[1] The underlying theoretical premise is that all coxibs are equally pro-thrombotic by virtue of their selective inhibition of COX-2 and that this is the sole cause of cardiovascular events. All coxibs, however, are not alike. There are substantial variations in the relative ability of the currently available coxibs to inhibit COX-2 (and COX-1) activity in laboratory assays.[14] (*See Figure 1.*) Rofecoxib is approximately nine times more potent in its ability to inhibit COX-2 relative to COX-1 than is celecoxib,[14] and high-dose celecoxib also may have a COX-1 blocking effect on platelet thromboxane production.[27] Regardless, the in vitro characteristics of the coxibs may not translate uniformly into equal effects in vivo.

The Clinical Studies

The CLASS trial (Celecoxib Long-term Arthritis Safety Study)[28,29] studied approximately 8000 patients receiving either high dose celecoxib (800 mg/day), ibuprofen (Advil, Motrin, Nuprin) 2400 mg/day, or diclofenac (Voltaren) 150 mg/day in patients with rheumatoid arthritis or osteoarthritis. Average time of exposure to drug was nine months. Twenty-one percent of patients were receiving aspirin for cardiovascular prophylaxis. No differences in rate of myocardial infarction or stroke were observed between the celecoxib and control groups. It is important to note that the investigators chose a very high study dose of celecoxib (800 mg/day). The subsequent FDA-approved dose of celecoxib was 200 mg/day for osteoarthritis, and up to 400 mg/day for rheumatoid arthritis. The FDA-approved dose for familial adenomatous polyposis is 800 mg/day.

Concerns about cardiovascular toxicity raised by the VIGOR study stimulated further investigation of both rofecoxib and celecoxib. A large retrospective analysis of the Tennessee Medicaid database[11] reported an increased coronary heart disease risk associated with high-dose rofecoxib (> 25 mg/day) use but not with low-dose rofecoxib, celecoxib, or traditional NSAID use. Another large retrospective study of a Canadian population failed to demonstrate significant differences in rates of myocardial infarction among new users of celecoxib, rofecoxib, naproxen, or other NSAIDs compared to controls.[10] A meta-analysis of 19,000 patients found no evidence of increased cardiovascular risk associated with celecoxib compared to nonselective NSAIDs or placebo.[30]

Data from the huge (1.4 million patients) FDA Kaiser Permanente study[13] that had demonstrated an increased risk of AMI associated with rofecoxib actually showed a slightly reduced risk of AMI associated with celecoxib (OR 0.86). High-dose rofecoxib use was greater than three times more likely than celecoxib to be associated with a serious cardiac event.[13] Another recent case control study of patients admitted to Pennsylvania hospitals with first, nonfatal MI found a reduced risk of AMI in users of celecoxib compared to non-NSAID users (OR 0.43).[31] Rofecoxib use (primarily 25 mg/day) was associated with a slightly greater risk of AMI (OR 1.16). Risk of MI in nonselective NSAID users was reduced (OR 0.61).[31]

In December 2004 the FDA halted the Adenoma Prevention with Celecoxib (APC) trial due to an approximately 2.5-fold increased risk of cardiovascular events in patients treated with celecoxib 400 mg/day compared to placebo.[32] The cardiovascular risk associated with celecoxib 800 mg/day was 3.4 times greater than placebo. This trial has not been published, and there has been no opportunity to analyze the data. Another ongoing clinical trial (the PreSAP cancer trial) using identical analysis to assess cardiovascular risk has been reported to show no increased celecoxib-associated cardiovascular risk compared to placebo.[32]

Naproxen

In late December 2004 the National Institutes of Health suspended the use of both naproxen and celecoxib in the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT trial).[33] This action was taken after naproxen 440 mg/day, but not celecoxib 400 mg/day, was associated with an increased risk of cardiovascular and cerebrovascular events compared to placebo. The FDA recommended that patients using naproxen take it for no more than 10 days, then contact their physicians for recommendations.

Valdecoxib

Valdecoxib is the most recent FDA-approved coxib, and cardiovascular risk data are less abundant compared to rofecoxib or celecoxib. A large meta-analysis was performed of 10 randomized trials of almost 8000 patients with osteoarthritis or rheumatoid arthritis receiving valdecoxib, diclofenac, ibuprofen, or placebo.[34] Study duration was from six weeks up to one year. There was no evidence of increased cardiovascular events in users of valdecoxib at either therapeutic or supratherapeutic doses compared to non-selective NSAIDs or placebo. This also was true when the data were analyzed for aspirin use or non-use. Another study compared the analgesic efficacy of valdecoxib and its IV prodrug form, parecoxib, to placebo in patients undergoing coronary artery bypass surgery.[35] There was a non-statistically significant trend toward increased cardiovascular complications in the paracoxib/valdecoxib-treated patients, and there were more sternal wound infections observed in the paracoxib/valdecoxib arm. A similar finding was observed in another unpublished study resulting in the issue of a warning by the manufacturer against the use of valdecoxib in patients undergoing coronary artery bypass surgery.[36]

Lumiracoxib

Lumiracoxib, a structural analogue of diclofenac, is a highly selective coxib being evaluated for approval by the FDA. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[37,38] compared it to naproxen and to ibuprofen in the treatment of osteoarthritis. In this study of more than 18,000 patients, there was a three- to four-fold reduction in ulcer complications compared to control NSAIDs, but no statistically increased risk for cardiovascular events in patients receiving lumiracoxib.[37,38]

No Proof of Coxib Class Effect

Taken altogether, available published studies do not show proof of a coxib class effect regarding cardiorenal and cardiovascular complications. Absence of proof, however, is not the same as proof of absence. Randomized controlled prospective trials are considered the gold standard in detecting differences between therapies. Unfortunately, neither the VIGOR nor CLASS study was sufficiently powered to detect small risks of cardiovascular events.[39] It was estimated that a study of 20,000 patients would be required to answer this question.[39] Equally daunting is the fact that clear evidence for cardiovascular risk required 18 months of exposure to rofecoxib in the APPROVe study.[14] Shorter studies may fail to exclude small but important risks. On February 18, 2005, an advisory panel, convened by the FDA to evaluate the safety of the coxibs, concluded that coxibs carry cardiovascular risks, with valdecoxib posing the greatest risk and celecoxib posing the least risk. Cardiovascular risk of celecoxib 200 mg/day was not seen. The panel recommended that the benefits of the coxibs continue to outweigh the risks, and that they should not be removed from the U.S. market. It also recommended that warnings be added to product labels and that further research be done.[40]

Table 1. Risk Factors for NSAID-Associated Gastroduodenal Ulcers

ESTABLISHED RISK FACTORS

- Advanced age
- History of ulcer
- Concomitant use of corticosteroids
- Higher doses of NSAIDs, including the use of more than one NSAID
- Concomitant administration of anticoagulants
- Serious systemic disorder

POSSIBLE RISK FACTORS

- Concomitant infection with *Helicobacter pylori*
- Cigarette smoking
- Consumption of alcohol

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Some observers[41] have condemned the entire class of coxibs but others caution against such an approach.[42,43] Solomon and Avorn point out that cerivastatin (a statin), troglitazone (a glitizone), and bromfenac (an NSAID) all were withdrawn from the market after initial FDA approval due to unacceptable toxicities.[43] Other members of their class have stood the test of time and remain as valuable treatment options.

Aspirin-NSAID Interactions

Many patients require both aspirin for cardiovascular prophylaxis and an NSAID. It is possible that NSAIDs could interfere with aspirin's antiplatelet effects, or that aspirin could negate the gastrointestinal-sparing properties of the coxibs. It has been demonstrated that, when ingested prior to aspirin, ibuprofen antagonizes aspirin's ability to irreversibly inhibit platelet aggregation.[44] By reversibly (temporarily) binding to the platelet COX-1 receptor, ibuprofen blocks aspirin's permanent acetylation of the platelet, allowing recovery of platelet thrombotic function with subsequent loss of cardioprotective effect. In contrast, rofecoxib, diclofenac, and acetaminophen (Tylenol) did not produce a similar effect.[44] Neither celecoxib nor valdecoxib demonstrates effects on platelet function as measured in vitro.[45,46] This limited data suggests that a coxib or diclofenac may be preferable to other NSAIDs in patients requiring low-dose aspirin for cardioprophylaxis.

Although the coxibs have shown a reduction in risk of gastroduodenal ulceration and complications compared to NSAIDs, this advantage could be eliminated in patients concurrently receiving low-dose aspirin. Although the CLASS[28,29] study compared ulcer complication rates in aspirin users receiving celecoxib or NSAIDs, it lacked the statistical power to definitively answer this question. Until larger and more definitive studies address this issue, those patients at high risk for upper gastrointestinal complications receiving both low-dose aspirin and a coxib may require prophylactic anti-ulcer therapy.

Table 2. Suggested Strategy for Analgesic/Anti-inflammatory Treatment and Cardiovascular Prevention in Patients with Varying Risks of Upper GI and Cardiovascular Complications

RISK OF VASCULAR EVENT	RISK OF SERIOUS UPPER GI COMPLICATIONS		
	Low (< 0.2% per year)	**Intermediate** (0.2-0.5% per year)	**High** (> 0.5% per year)
Low (< 1% per year)	NSAID or coxib, no ASA	Coxib, no ASA	Coxib, no ASA
Intermediate (1-3% per year)	NSAID, or coxib if ASA indicated	Coxib +/- low-dose ASA	Coxib +/- low-dose ASA
High (> 3% per year)	Coxib + low-dose ASA	Coxib + low-dose ASA	Coxib + low-dose ASA

Key:
NSAID = Nonsteroidal anti-inflammatory drug; ASA = aspirin

Anticoagulated Patients and NSAID Choice

The coxibs have little or no effect on platelet function, which may be useful in certain clinical situations such as patients receiving anticoagulant therapy. In one study of patients receiving warfarin, the risk of bleeding was approximately three times greater in patients taking nonselective NSAIDs compared to those taking coxibs.[47] This result was not seen in a more recent study comparing the risk of hospitalization for upper gastrointestinal hemorrhage in warfarin-receiving patients.[48] Patients taking rofecoxib or celecoxib had a similar risk of upper gastrointestinal bleeding compared to patients taking nonselective NSAIDs.

The Coxibs: Current Knowledge

Following are important summary points highlighting current clinical knowledge of coxib drugs.

• The coxibs are as effective but no more effective than nonselective NSAIDs in their ability to reduce pain and inflammation.

• The coxibs demonstrate less serious gastrointestinal toxicity with fewer symptomatic ulcers and their complications compared to nonselective NSAIDs. Many patients unable to tolerate previous antiinflammatory medicines have been able to take and tolerate a coxib. Some observers have postulated as much as a two-thirds potential reduction in gastrointestinal-related deaths as coxib use has supplanted non-selective NSAID use.[42]

• Rofecoxib, especially at doses higher than 25 mg/day, carries an increased risk of cardiovascular toxicity, primarily nonfatal AMI, particularly in patients with increased cardiovascular risk. The effect of rofecoxib on blood pressure, edema, and cardiovascular events appears dose-related. It has been voluntarily withdrawn from the market and is not currently available for use.

• The current evidence does not support a uniform coxib class effect in regard to increased cardiovascular events. It has not, however, conclusively ruled out this possibility. Further studies will be needed to definitively answer this important question.

• The coxibs, similar to nonselective NSAIDs, impact renal function, sodium retention, and blood pressure, most prominently in hypertensive patients treated with beta-blockers, angiotensin-converting enzyme inhibitors, and loop diuretics. This influence is not uniform; rofecoxib appears to have a greater effect compared to celecoxib, whose impact appears minimal.

• There is no conclusive evidence that NSAIDs such as naproxen are cardioprotective in a manner similar to aspirin. They should not be used as cardioprotective agents.

• Ibuprofen, but not rofecoxib or diclofenac, blocks aspirin's anti-platelet effects.

• Little is known about the cardiovascular effects of nonselective NSAIDs. They have not been studied nearly to the extent that the coxibs have in this regard. Switching a patient from a coxib (whose cardiovascular effect has been extensively, albeit imperfectly, studied) to a nonselective NSAID (which has received scant evaluation for cardiovascular safety) to avoid a cardiovascular event has no basis in logic and is, in effect, burying one's head in the sand.

Recommendations

Following are recommendations for treatment of patients with acute or chronic musculoskeletal conditions. They include strategies for patients at varying risk for upper gastrointestinal and cardiovascular complications.

• Physicians should avoid making treatment decisions based solely on media reports of unpublished preliminary data that have not been subjected to peer review. New reports must be

evaluated and placed in context with existing information. Without the benefit of this process, altering clinical decision-making may be harmful instead of helpful. Continue to consult treatment guidelines[49,50] published by respected groups and await new recommendations.

• Use nonpharmacological therapy, including patient education, physical and occupational therapy, assistive devices, and other therapies when appropriate.

• Consider acetaminophen for patients requiring analgesic but not an anti-inflammatory therapy. Acetaminophen in doses up to 4 g daily has been demonstrated to be effective in the treatment of mild to moderate osteoarthritis pain.[49] It should be used with caution in patients with liver disease or chronic alcohol abuse.

• Consider nonacetylated salicylates such salsalate or choline magnesium trisalicylate. These compounds lack significant prostaglandin inhibition yet still are effective analgesic and anti-inflammatory agents through other mechanisms.

• Patients requiring chronic use of NSAIDs should be evaluated based on their risks of cardiovascular disease and gastroduodenal toxicity. (*See Tables 1, 2.*) The patient at low risk for vascular events or upper gastrointestinal complications can be treated with either a nonselective NSAID or a coxib. If there is a history of sulfonamide drug allergy, the coxibs currently available in the United States cannot be used. Patients with known coronary heart disease, cerebrovascular disease, or who have sufficient risk factors for these diseases should be receiving low-dose aspirin. If a patient is taking low-dose aspirin and requires anti-inflammatory therapy, use of a coxib may be preferred due to lack of interference with aspirin's antiplatelet effect. Use of ibuprofen should be avoided in this situation. If a patient is at high risk for a cardiovascular event and cannot take aspirin or another antiplatelet agent, the use of a coxib should be avoided until further information is available as to its safety in this setting.

• Patients at high risk for upper gastrointestinal complications who require chronic use of NSAIDs should use a coxib if possible. If a nonselective NSAID is chosen, then gastroprotective agents such as misoprostol or a proton pump inhibitor should be used.

• Patients at high risk for both upper gastrointestinal complications and a cardiovascular event should use low-dose aspirin and a coxib if possible. As aspirin appears to negate the gastrointestinal-sparing benefit of a coxib, gastrointestinal prophylaxis with misoprostol or a proton pump inhibitor should be used.

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Physician CME Questions

23. Which drug has been demonstrated in vitro to block the anti-platelet effect of low-dose aspirin?
    A. Ibuprofen
    B. Choline magnesium salicylate
    C. Celecoxib
    D. Valdecoxib
    E. Naproxen

24. What is the theoretical basis of the concept of a coxib cardiovascular class effect?
    A. The coxibs, by blocking aspirin's effect on platelet thromboxane A_2 formation, negate aspirin's cardioprotective effect and increase thrombosis.
    B. Whereas the nonselective NSAIDs have an anti-inflammatory spectrum of activity that extends to the vasculature, the coxibs lack such an effect, leading to a greater frequency of myocardial infarction and cerebrovascular events.
    C. The coxibs have no beneficial gastrointestinal-sparing effects but have greater cardiovascular toxicity compared to nonselective NSAIDs.
    D. The coxibs, by their selective inhibition of endothelial cell prostacycline I_2 production in combination with unopposed platelet thromboxane A_2 formation, shift the balance of hemostasis toward thrombosis.

25. Regarding the benefit/safety profile of NSAIDs and coxibs, which statement is most accurate?
    A. The coxibs are both better anti-inflammatory drugs and exhibit less gastrointestinal toxicity compared to nonselective NSAIDs.
    B. The coxibs are equivalent anti-inflammatory drugs and exhibit less gastrointestinal toxicity compared to nonselective NSAIDs.
    C. The coxibs are less effective anti-inflammatory drugs but exhibit less gastrointestinal toxicity compared to nonselective NSAIDs.
    D. The coxibs are less effective anti-inflammatory drugs but exhibit less cardiovascular toxicity compared to nonselective NSAIDs.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

In Future Issues:

Alzheimer's Disease

26. When treating a patient on low-dose aspirin for secondary cardioprophylaxis who also requires an anti-inflammatory drug, which of the following is true?
    A. A coxib should not be used.
    B. An NSAID plus warfarin should be used.
    C. Diclofenac may be a reasonable choice.
    D. Ibuprofen may be a reasonable choice.

27. When treating a patient with prior history of ulcer who also requires an anti-inflammatory drug, which of the following is the best answer?
    A. A coxib should not be used.
    B. An NSAID plus a proton pump inhibitor is a reasonable choice.
    C. Aspirin for primary cardioprophylaxis should be discontinued.
    D. Acetaminophen is a reasonable choice.

28. Regarding NSAIDs and hypertension, which of the following statements is true?
    A. NSAIDs either have no effect on blood pressure or lower it.
    B. NSAIDs are more likely to elevate blood pressure in a patient with treated hypertension than in someone without hypertension.
    C. NSAIDs exert their greatest change in blood pressure in patients treated with calcium channel blockers.
    D. Loop diuretics block any untoward effect of NSAIDs on blood pressure.

29. By what percentage does aspirin reduce vascular events?
    A. 15
    B. 30
    C. 45
    D. 60
    E. 75

CME Answer Key

23. A
24. D
25. B
26. C
27. B
28. B
29. B

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Preparing for the Possibility of a Bird Flu Pandemic

The possibility of a bird flu pandemic has health officials worldwide in a high state of alert. The highly pathogenic avian influenza A virus is responsible for the death of more than 100 million birds in Southeast Asia, but less than 100 cases have been documented in humans, and only 2 of those have been from human-to-human contact. Still, influenza A viruses are known to undergo an antigenic shift periodically, marking an abrupt change in the viral genome. It is the possibility of a mutation that has health officials concerned. If the virus suddenly became infectious in human populations, the resulting pandemic could kill millions, as similar avian influenza virus pandemics did in 1968, with one to four million deaths, and 1918, when the avian flu pandemic killed as many as 50 million people. The World Heath Organization is urging all countries to develop or update their influenza pandemic preparedness plans. From a pharmaceutical perspective, the WHO has singled out oseltamivir (Tamiflu) as the treatment of choice to reduce symptoms and prevent spread of avian influenza. Roche Holding AG, the makers of oseltamivir, recently announced that Britain and the United States are discussing large purchases of the drug, with the intent of stockpiling supplies for a potential avian influenza outbreak. Other governments around the world have been stockpiling the drug as well, and Roche is increasing its production capacity to meet the additional demand.

Amoxicillin-Clavulanate vs Ciprofloxacin

The search for effective antibiotics to treat common infections is a high priority, given increasing resistance patterns for many commonly used antibiotics. This was the basis for a new study by researchers at the University of Washington, in which they compared ciprofloxacin to amoxicillin-clavulanate in women with uncomplicated cystitis. The study was driven by an increasing rate of resistance to trimethoprim-sulfa and other antimicrobials among *E. coli* strains causing acute cystitis in women. While ciprofloxacin is a common alternative, amoxicillin-clavulanate has not been well studied. In a randomized, single-blinded trial, 370 women aged 18 to 45 with symptoms of acute uncomplicate cystitis with a positive urine culture were randomized to amoxicillin-clavulanate 500/125mg twice daily or ciprofloxacin to 250 mg twice daily for 3 days. Clinical cure was observed in 58% of women treated with amoxicillin-clavulanate, compared with 77% of women treated with ciprofloxacin ($P < .001$). Amoxicillin-clavulanate was not as effective as ciprofloxacin, even among women infected with *E. coli* strains suscepti-

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ble to amoxicillin-clavulanate. At follow-up visits 2 weeks after treatment, 45% of women in the amoxicillin-clavulanate group had vaginal colonization with *E. coli*, compared to only 10% in the ciprofloxacin group ($P <$ .001). The authors point out that *E. coli* resistance is an increasing problem worldwide, especially with trimethoprim-sulfa. However, resistance is also been seen with fluoroquinolones including ciprofloxacin. Amoxicillin-clavulanate was chosen in the study in the hopes of finding an effective fluoroquinolone-sparing antibiotic for the treatment of uncomplicated cystitis. Unfortunately, amoxicillin-clavulanate is not a reliable option and alternatives will need to be found (*JAMA.* 2005;293:949-955).

AD Therapy and Cognitive Function

Men with prostate cancer who note worsening cognitive function in the early stages of androgen deprivation (AD) therapy should consider that the change is due to the treatment not the disease, according to new study published online in the "Early View" section of *Cancer*. Researchers from Finland followed 23 men undergoing AD for prostate cancer. Thirty-one cognitive tests were performed at baseline, 6 months, and 12 months into therapy. Testosterone and estradiol locals were followed throughout treatment. Visual memory of figures in recognition speed of numbers were significantly impaired at 6 months. Surprisingly, some men with the lowest change in estradiol levels had an improvement in verbal fluency and 12 months. The author suggests that cognition may be adversely affected during androgen deprivation (*Cancer*-published online 2/16/05).

LDL Lowering in CHD Patients

An LDL target in the 70s for CAD patients may become the standard, as evidence continues to mount for the benefit of intensive cholesterol lowering. The latest study from the "Treating to New Targets" or TNT investigators looked at 10,000 patients with stable coronary disease and LDL levels less than 130. Patients were randomized to atorvastatin 10 mg/day (low dose) or 80mg/day (high dose) and were followed for an average of 4 years. Mean LDL cholesterol was lowered to 101 mg/dL in the low-dose group and to 77 mg/dL in the high-dose group. Persistent elevations in liver enzymes was more common in the high-dose group (0.2% low dose, 1.2 % high dose [$P <$ .001]). The study end points were cardiovascular events including death from CHD, nonfatal MI, resuscitation after cardiac arrest, or stroke (fatal or nonfatal). A primary event occurred in 548 patients in the low-dose group (10.9%) and 434 patients in the high-dose group (8.7%) for a 2.2% absolute rate reduction (HR, 0.78; 95% CI, 0.69-0.89; $P <$ .001). There was a higher death rate from noncardiovascular causes in the high-dose treatment group, and no difference in overall mortality. There were no trends in the noncardiovascular deaths, specifically no higher rate of cancer or violent deaths. The authors conclude that aggressive LDL lowering is warranted in CHD patients (*N Engl J Med*-published online March 2005). An accompanying editorial suggests more caution, stating, "Patients and their physicians will need to carefully weigh the benefits or a reduction in the risk of cardiovascular events. . . against the uncertainty of an increase in the risk of death from noncardiovascular causes" (*N Engl J Med*-published online March 2005).

FDA Actions

The FDA and federal marshals from the Department of Justice have seized Paxil CR and Avandamet tablets manufactured by GlazxoSmithKline at its plants in Knoxville, TN, and Puerto Rico. The FDA stated that the seizures were prompted by violations of manufacturing standards that resulted in the production of poor quality drug products, including tablets that could split apart and tablets that had inaccurate doses of the active ingredient.

In late February, the FDA issued a public health advisory regarding nataluzimab (Tysabri), Biogen's recently approved drug for the treatment of relapsing forms of multiple sclerosis. Marketing of the drug has been suspended while the agency and the manufacturer evaluate 2 cases of progressive multifocal leukoencephalopathy in MS patients who were using the drug, one of which resulted in death. Nataluzimab received accelerated approval in November 2004, and 8000 patients have received the drug, including 3000 who received it during clinical trials. ■