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COX 2-selective NSAIDs: Biology, promises, and concerns

■ ABSTRACT

Celecoxib (Celebrex) is the first of a new family of nonsteroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit cyclooxygenase 2 (COX 2) while sparing COX 1. Clinical trials indicate that it is approximately as effective in relieving the pain of osteoarthritis and the pain and inflammation of rheumatoid arthritis as nonselective NSAIDs, but causes less gastrointestinal ulceration and bleeding. This paper reviews the pharmacology and possible clinical role of celecoxib and other COX 2-selective NSAIDs.

■ KEY POINTS

COX 2-selective NSAIDs do not inhibit platelet function, and so may be good choices in patients with thrombocytopenia who require NSAID therapy.

COX 2-selective NSAIDs offer a distinct safety advantage over most nonselective NSAIDs in patients who are at high risk for gastric complications, but they should not be assumed to be totally without gastric complications.

The primary question in determining whether a patient needs a COX 2-selective NSAID is whether he or she needs any NSAID in the first place—another drug or a nonpharmacologic approach may be more appropriate.

For a more comprehensive reading and reference list, see the *Cleveland Clinic Journal of Medicine* web site at: www.ccm.org/cox2ref.htm.

THE CYCLOOXYGENASE (COX)-2 inhibitors are a new family of nonsteroidal anti-inflammatory drugs (NSAIDs) designed specifically to limit the side effects of gastric erosions, ulcerations, and bleeding that occur with other NSAIDs. One such drug—celecoxib (Celebrex)—is already available, and others are in development.

In the pages that follow I review the pharmacology of these new drugs and offer my perspective on their clinical role, which I would sum up as follows: they do offer a substantial safety advantage, but we should not assume they will be completely harmless. The first question to ask is not whether your patient needs a COX 2-selective NSAID, but whether he or she needs any NSAID or if an analgesic or disease-modifying drug might be more appropriate.

■ THE PROBLEM: NSAID-INDUCED GASTROPATHY

NSAIDs are generally well tolerated, but they have predictable side effects, including gastropathy, especially in certain groups (TABLE 1).

In clinical trials, approximately 20% of patients who took NSAIDs for even short periods developed gastric erosions that were detectable on endoscopy. Fewer than 10% of these endoscopic lesions lead to clinically significant events.¹ However, so many people take NSAIDs that even uncommon clinical events have a significant financial and societal impact. Case-control studies show that persons admitted to the hospital because of upper gastrointestinal bleeding or complications of gastric ulcers are more likely to have been taking prescribed or over-the-counter NSAIDs than are matched controls.²

*Disclosure: Dr. Mandell has received personal honoraria, support for educational programs, or research support from Amgen, Ciba-Geigy (Novartis), Merck, Searle, Smith Kline Beecham, and Wyeth Pharmaceuticals.

TABLE 1

Risk factors for gastrointestinal complications from NSAIDs

Elderly patients
High doses or multiple NSAIDs (including low-dose aspirin therapy)
Anticoagulant therapy
Comorbid medical conditions, including rheumatoid arthritis
History of peptic ulcer disease or use of H₂ antagonists
Cardiovascular disease (even higher risk in those taking aspirin)

■ NSAIDS INHIBIT CYCLOOXYGENASE

NSAIDs inhibit cyclooxygenase (COX), a rate-limiting enzyme in the pathway that synthesizes prostaglandins such as prostaglandin E, prostacyclin, and thromboxanes.³ Since prostaglandins mediate not only certain aspects of inflammation but also renal blood flow, hemostasis, and gastric "cytoprotection," at first it did not seem possible to produce an effective NSAID that was free of adverse effects.

■ COX 1, COX 2, AND THE COX HYPOTHESIS

In the early 1990s, researchers discovered that COX exists in two isoforms: COX 1 and COX 2 (reviewed by Smith and DeWitt⁴). The genes for the two forms are on separate chromosomes, the two forms are present in various amounts in different organs, and they serve distinct, although occasionally redundant, biologic functions.

Platelets contain only COX 1, but many other tissues express COX 1 in their resting state. In contrast, although specific areas of the brain and kidney manufacture COX 2 in their resting states, COX 2 is more frequently expressed in several tissues as part of an activation response to cytokines, growth factors, or local injury. Glucocorticoids inhibit mRNA synthesis of COX 2 but not COX 1. Nonselective NSAIDs inhibit the enzyme activity of both isoforms.

These observations led to the "COX hypothesis," ie, the notions that:

- COX 1 products are responsible for normal homeostasis ("housekeeping" func-

tions), while COX 2 products are responsible for modulating dynamic processes such as inflammation;

- Inhibition of COX 1 is primarily responsible for the organ-specific toxicity of nonselective NSAIDs, and in particular that gastric injury is solely related to inhibition of COX 1-generated prostaglandin E, since COX 1 is the predominant form of COX in healthy gastric mucosa, and exogenous prostaglandin E is capable of protecting against NSAID-induced gastric injury; and

- NSAIDs that selectively inhibit COX 2 would provide effective and safe anti-inflammatory therapy.

■ WHY THE COX HYPOTHESIS IS OVERSIMPLISTIC

In the intervening years, as more research was performed in animals and as COX 2-selective NSAIDs were developed, it was recognized that the initial COX hypothesis was an oversimplification. The roles of COX 1 and COX 2 vary among animal species, but studies in animals nevertheless expand their possible role in humans. Among the recent findings:

COX 1 inhibition is not the *only* factor in NSAID-induced gastropathy

In the initial COX hypothesis, it was assumed the COX 1 was required for gastric protection and COX 1 inhibition by NSAIDs caused gastric pathology. We now know that although COX 1 inhibition plays a significant, perhaps preeminent, role in causing NSAID-induced gastropathy, it is not the only factor. Two lines of evidence support this conclusion.

- Clinical trials and post-marketing studies suggest that some nonselective NSAIDs (nabumetone, etodolac) are less likely to cause gastropathy than other nonselective NSAIDs. Gastrointestinal safety is thus likely also related to drug properties such as potency, enterohepatic circulation, penetration through cytoprotective barriers, and the concentration of the drug in the gastric mucosa.

- "Knockout" mice that lack the gene for COX 1 (and therefore do not express COX 1 at all) do not develop spontaneous gastropathy, but still develop gastric ulcers when given the nonselective NSAID indomethacin.⁵

So many people take NSAIDs that even rare events add up

The IC₅₀ does not relate directly to clinical efficacy

WITH THE APPROVAL of COX 2-selective NSAIDs for clinical use, physicians may see discussions of the relative merits of these agents expressed in terms of a value called the IC₅₀.

In brief, the IC₅₀ is an in vitro measurement—the concentration of a substance that, under controlled conditions, inhibits 50% of the action of another substance. In this case, it is the concentration of a particular NSAID required to

inhibit 50% of the enzyme activity of COX 1 or COX 2, depending on which is being measured.

Clinicians should understand that the IC₅₀ does *not* predict the actual amount of enzyme inhibition (potency) in vivo, nor does it directly translate into a measure of clinical efficacy. The utility of the IC₅₀ is to compare, under in vitro circumstances, the *efficiency* of inhibition, not the potency or actual clinical effect.

COX 1 may play a role in inflammation and analgesia

In some animal models of inflammation, COX 1 mediates some of the inflammation.⁶ The human counterparts to these studies, however, have not been identified.

COX 2 plays more roles than once thought

COX 2 serves a greater biologic role than simply mediating pain and inflammation, as demonstrated in animals that lack the COX 2 gene and also with the use of COX 2-selective inhibitors in animals. In particular, COX 2 plays a role in:

- Gastric mucosal healing in chemical-induced injury⁷ and in colitis.⁸ (There are no published data on surgical wound healing.)
- Bone remodeling (possibly)⁹
- Gastric adaptive cytoprotection¹⁰
- Modulating renal function in some animals (although this role is not fully defined in humans).

COX 2 may also promote cellular proliferation. Selective COX 2 inhibitors (like some nonselective NSAIDs) decrease colonic polypoidosis and the development of colon adenocarcinoma in animals,¹¹ and I expect they will have a similar effect in humans, since many nonselective NSAIDs decrease the frequency of colon cancer in humans.

COX 2-selective NSAIDs may not be totally without adverse effects

Clinical trials have demonstrated that COX 1-sparing NSAIDs are less injurious to the gastric mucosa than are nonselective NSAIDs,¹²

but we should not assume that they are totally without adverse effects, especially in the presence of coincident gastric injury.

On the other hand, it seems unlikely that COX 2-selective NSAIDs will cause *more* side effects than nonselective NSAIDs, except perhaps in situations in which the balance between COX 1 and COX 2 is of paramount importance in maintaining homeostasis. Such situations have yet to be clinically identified, but in theory include thrombosis at the site of atherosclerotic or injured endothelium, where selective COX 2 inhibitors decrease prostacyclin generation, leaving prothrombotic platelet-derived thromboxane untouched.¹³ Preliminary unpublished data from clinical trials of two selective COX 2 inhibitors suggest that there is no dramatically increased rate of thrombosis.

The animal studies noted above illustrate the need for long-term clinical studies in high-risk patients to demonstrate the improved safety of these drugs.

CLINICAL EFFECTS OF COX 2-SELECTIVE NSAIDS

What do we know about use of COX 2-selective NSAIDs in humans—and what do we *not* know? TABLE 2 summarizes the discussion below.

Efficacy in chronic pain

Clinical trials have demonstrated that COX 2-selective NSAIDs relieve the discomfort of osteoarthritis of the knee and hip as effectively as nonselective NSAIDs such as diclofenac,

For analgesia alone, first consider acetaminophen or a mild narcotic analgesic

**TABLE 2****Qualitative comparison of nonselective and COX 2-selective NSAIDs**

	NONSELECTIVE NSAIDs	COX 2-SELECTIVE NSAIDs
Incidence of side effects		
Gastric ulcers, bleeding, perforation, obstruction	Uncommon*	Close to placebo rate [†]
Decreased platelet function	Common	None
Decreased renal function (reversible) in patients at risk	Uncommon	Unknown
Bronchospasm (in sensitive patients)	Uncommon	Unknown
Central nervous system side effects	Rare*	Unknown
Efficacy in treating:		
Acute pain	Moderate*	Unknown
Pain in chronic osteoarthritis	Moderate	Moderate
Pain in chronic rheumatoid arthritis	Moderate	Moderate
Pain in acute migraine	Moderate*	Unknown
Pain in chronic spondylitis	Mild*	Unknown
Pain in acute gout	Strong*	Unknown
Approved for children	Yes*	No

*Differs among individual NSAIDs

[†]Longer follow-up of patients using these drugs is required

ibuprofen, and naproxen given in anti-inflammatory doses. Comparable efficacy has also been demonstrated in patients with rheumatoid arthritis, although published studies with celecoxib were relatively short, lasting months, not years.¹²

Of note: most of these studies only included patients who had clearly responded previously to other NSAIDs. In the general population the response rate can be expected to be lower, but not necessarily lower than with other NSAIDs.

Moreover, for the provision of analgesia, inhibition of COX 2 in the spinal cord may be even more important than inhibiting it at the site of inflammation.¹⁴ Thus, the ability to penetrate into the CNS may influence the efficacy of individual drugs.

Will they relieve acute pain and gout?

We have less evidence that COX 2-selective inhibitors are effective in relieving acute pain not due to “flares” subsequent to withdrawal of NSAID therapy. In unpublished studies, these drugs demonstrated some analgesic effect in relieving the acute pain of molar extraction.

The degree of analgesia achieved with celecoxib was greater than with placebo, but perhaps slightly less than with nonselective NSAIDs such as naproxen or ibuprofen at early time points. Rofecoxib is more effective than placebo, and equally efficacious as nonselective NSAIDs in the relief of pain following molar extraction.¹⁵ Additional studies are also underway with celecoxib. The time of onset and degree of analgesia in specific situations need to be closely studied before these medications are broadly used for acute analgesia.

There are no data addressing the utility of COX 2-selective NSAIDs for treating acute crystal-induced arthritis, ie, gout. While I expect that they should be effective, their potency and time to onset of effect will be critical issues. Individual agents will need to be evaluated, rather than assuming they all have clinical utility in this setting. These drugs may offer an advantage for chronic maintenance therapy in older patients with chronic gout who cannot tolerate colchicine, or who achieve a less than optimal benefit from this drug but have a high risk for complications with nonselective NSAIDs.

We have little data about using COX 2 inhibitors to treat acute pain

Clinical use of celecoxib

CELECOXIB (Celebrex) is a cyclooxygenase 2-selective NSAID.

INDICATIONS

Celecoxib is approved by the Food and Drug Administration for treating osteoarthritis and adult rheumatoid arthritis. Additional studies of its use as an acute analgesic are underway.

PHARMACOKINETICS

The drug is metabolized in the liver by cytochrome P450-2C9. Very little unchanged drug is excreted in urine or feces. An altered glomerular filtration rate does not interfere with the drug's clearance. Celecoxib does not interfere with the metabolism of methotrexate or warfarin. It is 97% protein-bound.

CAUTIONS AND ADVERSE EFFECTS

Celecoxib does not seem to cause hepatotoxicity, but has not been fully evaluated in patients with hepatic insufficiency, or with long-term use in the very elderly. The trials in patients with osteoarthritis have included elderly patients without demonstrable age-related problems.

Celecoxib may interfere with renal function, perhaps to a similar degree as other NSAIDs, and should be avoided or used with caution in patients

with renal insufficiency or significantly decreased renal perfusion until additional data are available.

Although no studies have been conducted in pregnant women, celecoxib should be avoided in patients in the third trimester of pregnancy and in nursing mothers.

Asthmatic patients with bronchospasm or rhinitis made worse by aspirin or NSAIDs should not take this drug.

Celecoxib should be avoided in patients with known allergy to sulfonamides.

Because the trade name for celecoxib—Celebrex—resembles several other drugs, notably Celexa (citalopram hydrobromide, an antidepressant) and Cerebyx (fosphenytoin, an anticonvulsant), physicians are advised to be especially careful when writing a prescription or giving a verbal order.

DOSAGE

Osteoarthritis—200 mg once a day or 100 mg twice a day.

Adult rheumatoid arthritis—100–200 mg twice a day.

Higher doses did not increase the efficacy in clinical trials. The drug can be taken before or after meals, with a slightly delayed rate of absorption if taken with a fatty meal.

COX 2-selective NSAIDs cause less gastropathy than other NSAIDs

Clinical trials demonstrated that the COX 2-selective NSAIDs celecoxib and rofecoxib cause far fewer acute gastric erosions seen on upper endoscopy than did several nonselective NSAIDs.¹³ More important, in trials lasting 3 months that were presented to the FDA, the occurrence of clinically significant perforations, gastric obstructions, and upper GI hemorrhages was significantly less with celecoxib than with the nonselective NSAIDs diclofenac, ibuprofen, or naproxen, close to the rate seen with placebo.

Longer evaluation with general use is needed to determine whether the delayed mucosal healing caused by COX 2-selective inhibition seen in animals has any clinical rel-

evance. We should not assume that COX 2-selective NSAIDs will be totally devoid of toxicity in patients with prior GI mucosal problems such as *Helicobacter pylori* infection. Clinical studies are underway to address this issue.

Are they safe in perioperative patients?

COX 2-selective NSAIDs do not affect platelet aggregation or bleeding time. However, these are surrogate markers—the real issue is clinically significant bleeding episodes.

Bleeding time and platelet aggregation studies do not provide sufficient information to predict postoperative bleeding complications,¹⁶ and no clinical trials to date have indicated that COX 2-selective NSAIDs have any advantage over nonselective NSAIDs in



terms of perioperative bleeding complications. (Some studies have failed to demonstrate that aspirin or nonselective NSAIDs adversely affect perioperative bleeding, although preoperative administration of the nonselective NSAID ketorolac has recently been shown to increase bleeding in children undergoing tonsillectomy.¹⁷)

COX 2-selective NSAIDs given before anesthesia conceivably may improve postoperative pain control without increasing bleeding, but this will need to be formally studied to see if they do so safely and as effectively as narcotics or other nonnarcotic analgesics. If an NSAID is required in the perioperative setting, a COX 1-sparing NSAID would seem to be the reasonable choice.

Are they safe in patients receiving warfarin?

Celecoxib does not interfere with the INR in patients receiving long-term warfarin therapy. (Neither do the nonselective NSAIDs oxaprozin and nabumetone.) However, if the new COX 2-selective NSAIDs even slightly increase the risk of gastric injury or decrease healing of coexistent mucosal ulcerations, their co-administration with warfarin could still in theory increase the risk of clinically significant gastrointestinal bleeding. Celecoxib should still be safer in this setting than nonselective NSAIDs.

Other questions and concerns

Do they affect renal function? Steady-state and inducible expression of COX 2 in the kidney has been demonstrated in some animal studies, although renal COX 2 expression is very species-dependent. A preliminary study of celecoxib in humans demonstrated only slight adverse physiological effects on renal function in salt-depleted patients.¹⁸ Whether the COX 2-selective drugs will cause decreased renal function in patients with renal insufficiency or flow-related type 4 renal tubular acidosis remains to be seen. There is no reason to expect any increased renal complications from these drugs compared with nonselective NSAIDs. Differences in the propensity of different NSAIDs to cause renal insufficiency may be due to differential access or penetration into renal cells.

Do they induce bronchospasm? Nonselective NSAIDs can induce bronchospasm, particularly in patients with asthma or rhinitis made worse by aspirin. There have been no published data on the relative risk of this occurring in patients given COX 2-selective inhibitors. However, there is no a priori reason to believe that these drugs cannot elicit such an adverse response, and they should be avoided in patients with the triad of aspirin sensitivity, nasal polyposis, and asthma until their safety is assessed.

Other concerns. The controversial possibility that cartilage damage in patients with osteoarthritis may be accelerated by certain NSAIDs has not been fully explored with COX 2-selective drugs.

Some elderly patients suffer confusion from even low doses of propoxyphene, tramadol, and some NSAIDs (eg, indomethacin). Since COX 2 is present in the brain and brain blood vessel walls, this may be a similar problem, though uncommon, with selective drugs.

The new COX 2-selective NSAIDs still seem to be variably associated with some of the nuisance side effects exhibited by currently available NSAIDs such as dyspepsia and diarrhea, but not to a major degree in clinical trials. The significance of these nuisance symptoms will need to be evaluated in post-marketing surveillance studies. Whether there will be any significant differences between the COX 2-selective NSAIDs remains to be determined.

RECOMMENDATIONS

The first decision facing the physician when deciding whether to use one of the newer NSAIDs remains whether *any* NSAID is the most appropriate therapy.

If analgesia is the goal, first consider using acetaminophen or a mild narcotic analgesic, for reasons of cost, safety, and extensive clinical experience using these drugs. When treating inflammation, the specific disease needs to be evaluated and the requirement for anti-inflammatory therapy should be individually assessed. For example, in patients with chronic inflammatory diseases such as rheumatoid arthritis, consider the benefits of

COX 2-selective NSAIDs cannot replace aspirin for cardiovascular protection



using disease-modifying drugs. NSAIDs, which provide partial symptom relief, should not be used instead of appropriately dosed disease-modifying agents, appropriate exercise, and orthotics.

Does the patient need a selective NSAID?

In prescribing a COX 2-selective NSAID instead of a nonselective NSAID (with or without a gastric protective drug such as a proton pump inhibitor or misoprostol), the clinician should consider efficacy and cost of the NSAID, and the possibility of additional side effects and cost of the protective drug (eg, diarrhea from misoprostol).

In a patient with a high risk for gastropathy, COX 2-selective NSAIDs will provide useful alternatives to combination therapy with a gastric protective drug and a nonselective NSAID. However, in a patient at very low risk, it is difficult to justify using a more expensive drug with equivalent efficacy, especially for short-term use.

The COX-1-sparing drugs have an obvious advantage over the nonselective

NSAIDs in patients with mild or moderate thrombocytopenia who require NSAID therapy, but this benefit will be lost if these patients require low-dose aspirin therapy for vascular protection. Similar platelet-sparing effects can be obtained with less-expensive, nonacetylated salicylates. The COX 1-sparing NSAIDs will likely offer no cardiovascular protective activity and cannot replace low-dose aspirin.

The monthly cost to the patient is approximately the same or less with celecoxib than with a generic NSAID plus a proton pump inhibitor, slightly greater than with a generic NSAID plus twice-daily doses of misoprostol, and much more expensive than using a generic NSAID alone. Thus, using a COX 2-selective drug alone is a reasonable financial choice in those high-risk GI patients who require coadministration of a proton pump inhibitor with a nonselective NSAID in order to limit the symptomatic side effects of the NSAID.

SEE OUR WEB SITE. For a more complete reference list, see www.ccjm.org/cox2ref.htm.

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