Commentary

COX-2: where are we in 2003?

Be strong and resolute: continue to use COX-2 selective inhibitors at recommended dosages in appropriate patients

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Abstract

Cyclooxygenase (COX)-2 selective inhibitors have been shown to have comparable efficacy to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Large outcome studies have shown that patients with OA and RA not taking low-dose aspirin have fewer symptomatic and complicated upper GI events when treated with COX-2 selective inhibitors than with nonselective NSAIDs. When used in recommended dosages, there is no convincing evidence that patients treated with COX-2 selective inhibitors have an increased incidence of cardiovascular thrombotic events, including non-fatal myocardial infarction, than patients treated with either placebo or nonselective NSAIDs other than naproxen. Co-therapy with low-dose aspirin is recommended in patients with OA and RA at increased risk for cardiovascular events; the need for gastroprotective therapy in such patients is controversial.

Keywords: celecoxib, COX-2 selective inhibitors, osteoarthritis, rheumatoid arthritis, rofecoxib

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of therapy for relief of pain and inflammation in patients with acute and chronic musculoskeletal diseases, particularly osteoarthritis (OA) and rheumatoid arthritis (RA). The use of these drugs is limited, however, primarily by their toxicity. Nonselective NSAIDs (i.e. those that inhibit both cyclooxygenase [COX]-1 and COX-2 [see below]) are associated with an increased risk for serious upper gastrointestinal (GI) complications, including perforation, symptomatic ulcers and bleeding (PUBs); nephrotoxicity, including edema, hypertension, and acute renal insufficiency; and congestive heart failure [1,2].

After the discovery in the late 1980s of a second isoform of cyclooxygenase, it was proposed that the COX-1 isoenzyme is expressed constitutively and the COX-2 isoenzyme is induced at sites of inflammation; hence, prostaglandins synthesized by COX-1 were suggested to be responsible for 'housekeeping' functions in the GI tract, kidney, and platelet, while those synthesized by COX-2 were responsible for pain and signs of inflammation in patients with arthritis. This led to the development of the 'COX-2 hypothesis': that NSAIDs that inhibit the COX-2 but not the COX-1 enzyme at therapeutic plasma concentrations would have the beneficial anti-inflammatory and analgesic effects but not the gastrointestinal or renal toxicity of nonselective NSAIDs [3]. The hypothesis was revised after the discovery that COX-2 was constitutively expressed in the kidney [4], to include protection only from GI complications, including PUBs.

Efficacy and GI safety of COX-2 selective inhibitors

Four COX-2 selective inhibitors have been approved and are marketed for use in the treatment of patients with OA and RA in some European, North American, and Latin American countries (Table 1); a fifth compound, lumira-

CLASS = Celecoxib Long-term Arthritis Safety Study; COX = cyclooxygenase; FDA = Food and Drug Administration; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs; OA = osteoarthritis; PUBs = perforation, symptomatic ulcers, and bleeding; RA = rheumatoid arthritis; VIGOR = Vioxx Gastrointestinal Outcomes Research.

coxib (Prexige [Novartis, Basel. Switzerland]), is currently in phase III development. Schnitzer and Hochberg reviewed the phase II and III randomized, controlled trials of these agents and concluded that all were more efficacious than placebo and all had similar efficacy compared with nonselective NSAIDs when used in therapeutic doses [5]. The single exception was one study that showed that etoricoxib at 90 mg per day was more efficacious than naproxen at 500 mg twice daily in patients with RA [6]. Thus, the first part of the COX-2 hypothesis is satisfied.

Acceptance of the second part of the COX-2 hypothesis requires the demonstration that patients treated with COX-2 selective inhibitors have fewer clinically important upper GI complications, especially complicated PUBs, than patients treated with nonselective NSAIDs. Two large outcome studies were conducted to test this hypothesis: the Vioxx Gastrointestinal Outcomes Research (VIGOR) Trial [7] and the Celecoxib Long-term Arthritis Safety Study (CLASS) [8]. Updated information on both of these studies was reported to the US Food and Drug Administration (FDA) Arthritis Advisory Committee in February 2001 (www.fda.gov/ohrms/dockets/ac/cder01.htm#Arthritis).

In the VIGOR trial, patients who received rofecoxib (50 mg per day) had significantly lower rates of both clinically important upper GI events (PUBs, the primary outcome) and complicated PUBs (the key secondary outcome) than patients treated with the nonselective NSAID naproxen at a dose of 500 mg twice a day: the respective relative risks (95% confidence intervals) were 0.46 (0.33, 0.64) and 0.43 (0.24, 0.78) [7].

In the CLASS, the rates of complicated PUBs (the primary outcome) were not significantly different between patients treated with celecoxib (400 mg twice a day) and the pooled NSAID comparators, diclofenac (75 mg twice a day) and ibuprofen (800 mg three times a day). Patients treated with celecoxib did, however, have a significantly lower incidence of the secondary outcome, symptomatic and complicated ulcers (PUBs), than did patients taking the nonselective NSAIDs. In the preplanned analyses comparing individual NSAIDs, the differences between celecoxib and ibuprofen were significant while those between celecoxib and diclofenac were not. In a post hoc analysis limited to patients not taking low-dose aspirin, the rate of both the primary and secondary outcomes was significantly lower in patients receiving celecoxib compared with patients receiving ibuprofen but not compared with patients receiving diclofenac.

Differences between the designs of these studies, particularly patient inclusion and exclusion criteria, choice of comparator NSAIDs, choice of primary and secondary outcomes, and underlying assumptions about reductions in risks for the primary outcome that were used to estimate sample size, have been noted by several authors to possibly explain the disparate results [9–11]. In addition to highlighting the potential flaws in the design of CLASS that might have explained the lack of achieving the primary outcome, Juni and colleagues also questioned the validity of the results [12]. A subsequent meta-analysis of nine randomized, controlled trials of celecoxib lasting 12 weeks or longer confirmed the GI safety of celecoxib compared with nonselective NSAIDs [13]; however, this meta-analysis included only the 6-month data published by Silverstein and colleagues [8] and did not include the entire data presented at the FDA hearing. From my own review of the data [9], I concluded that the COX-2 selective inhibitors celecoxib and rofecoxib did fulfil the 'revised' COX-2 hypothesis.

Table 1

COX-2 selective inhibitors currently marketed in some European, North American, and Latin American countries

Generic name	Proprietary name	Manufacturer
celecoxib	Celebrex	Pharmacia Corporation and Pfizer, Inc
etoricoxib	Arcoxia	Merck & Co, Inc
rofecoxib	Vioxx	Merck & Co, Inc
valdecoxib	Bextra	Pharmacia Corporation and Pfizer, Inc

Does this GI safety advantage extend to the newer COX-2 selective inhibitors? Data from a meta-analysis of phase II and III studies of etoricoxib also demonstrate a significantly lower rate of PUBs in patients treated with this COX-2 selective inhibitor than in those treated with nonselective NSAID comparators [14]. A similar meta-analysis including studies of valdecoxib is anticipated. Lumiracoxib is currently being studied in a large outcome study designed to enroll 18,000 patients.

Unresolved issues

On the basis of these data, one should recommend that COX-2 selective inhibitors be used in patients with arthropathies, especially OA and RA, who are at increased risk for upper GI complications from nonselective NSAIDs [15]. Established risk factors for the development of PUBs in patients treated with nonselective NSAIDs include age ≥65, a history of peptic ulcer disease or of upper GI bleeding, concomitant use of oral corticosteroids or anticoagulants, and, possibly, smoking and alcohol consumption [16–18]. Fendrick stated that the "unrestricted access to COX-2 selective inhibitors could be both clinically and economically advantageous because of the high likelihood of …safety benefits from coxibs" and suggested that "COX-2 selective inhibitors should be offered as first-line therapy to these high-risk patients" [19].

Unfortunately, the reality of the situation in the autumn of 2002 is not that simple. Two major questions remain unanswered: 1) are COX-2 selective inhibitors associated with an increased risk of cardiovascular thrombotic events? and 2) does concomitant therapy with low-dose aspirin, used for cardioprotection, eliminate the safety benefit of COX-2 selective inhibitors in comparison with nonselective NSAIDs?

The first question is based on the surprising finding in the VIGOR trial that patients who received rofecoxib had higher risk of cardiovascular thrombotic events, particularly nonfatal myocardial infarction, than patients who received naproxen [7]. Fitzgerald and Patrono proposed three hypotheses to explain these results: an antithrombotic effect of naproxen, a prothrombotic effect of rofecoxib, and the 'play of chance' [20]. Five observational epidemiologic studies published in the past 2 years examined the effect of NSAIDs, particularly naproxen, on the risk of cardiovascular thrombotic events including myocardial infarction; these studies were reviewed recently by Strand and Hochberg [21]. The results of a majority of these studies are consistent with a modest protective effect of naproxen on the development of nonfatal myocardial infarction; indeed, Dalen, in his editorial accompanying the three papers published in the *Archives of Internal Medicine*, concluded that the most likely explanation of the results in the VIGOR trial was "that naproxen decreases the incidence of acute myocardial infarction" [22]. Patrono suggested that a combination of a protective effect of naproxen and the "play of chance" operating in a short-term study [median follow-up of 9 months] with small numbers of events in a low-risk population [event rate below 1% per year] explained the findings in the VIGOR trial (Patrono C, Invited Lecture on 28 October 2002 at annual meeting of American College of Rheumatology, New Orleans, LA). Two meta-analyses have failed to demonstrate an increased risk of cardiovascular thrombotic events in patients receiving rofecoxib at doses ranging from 12.5 to 50 mg per day in comparison with both placebo and nonselective NSAIDs other than naproxen [23,24]. However, the dose of rofecoxib in the VIGOR trial was double the highest FDA-approved dose for chronic treatment in both OA and RA, and there were small numbers of patients treated who received this dose in the phase II and III OA and RA trials in which naproxen was not used as a comparator. Ray recently published results of a retrospective cohort study using data from the Tennessee Medicaid database and reported that new users of rofecoxib at doses greater than 25 mg per day had almost a twofold increased risk of serious cardiovascular events in comparison with controls not receiving NSAIDs, while users of rofecoxib at doses of 25 mg per day or less had no increased risk of such events [25]. The results of a meta-analysis of data from 15 controlled trials of celecoxib involving over 30,000 patients failed to demonstrate an increased risk of cardiovascular thrombotic events in patients who received celecoxib compared with those who received placebo or nonselective NSAIDs including naproxen [26]. Similarly, the results of an analysis of pooled data from four randomized, controlled trials of valdecoxib in over 3000 patients with RA failed to demonstrate an increased risk of cardiovascular thrombotic events [27].

Thus, it is unlikely that this increased risk is a class effect of COX-2 selective inhibitors when used in therapeutic doses. It seems prudent, however, not to use doses higher than those recommended for chronic therapy – i.e. rofecoxib 12.5 or 25 mg per day, celecoxib 200 or 400 mg per day, or valdecoxib 10 mg per day. Insufficient data are available at present to make definitive statements about the use of etoricoxib, other than to note that at recommended doses of 60 or 90 mg per day for chronic therapy of OA and RA, respectively, there is no apparent increased risk of cardiovascular thrombotic events in comparison with placebo and, in patients with RA, there is a reduced risk of such events in patients randomized to naproxen, the comparator NSAID in the phase III trials (Arcoxia Product Information, Merck & Co, Inc, Whitehouse Station, NJ, USA).

Use with low-dose aspirin

It is known that COX-2 selective inhibitors do not inhibit platelet aggregation, and hence low-dose aspirin should be used when appropriate for cardioprotection [15]. The indications for use of low-dose aspirin for primary and secondary prevention of cardiovascular disease are beyond the scope of this commentary. Nonetheless, if low-dose aspirin is used in conjunction with a COX-2 selective inhibitor in a patient at increased risk for both upper GI complications from nonselective NSAIDs and cardiovascular thrombotic events, the safety of this combination needs to be determined. There are at present insufficient data to draw conclusions about this question. In CLASS, the annualized incidence, based on the 6-month data, of complicated and complicated plus symptomatic ulcers in patients taking low-dose aspirin was, respectively, 2.0 and 4.7 per 100 for patients taking celecoxib, and 2.1 and 6.0 per 100 for patients taking comparator NSAIDs [8]. In addition, patients taking celecoxib and low-dose aspirin had a fourfold higher rate of complicated ulcers than patients taking celecoxib alone [8]. These data suggest that low-dose aspirin modified the effect of celecoxib in comparison with nonselective NSAIDs. Comparable data are not available for rofecoxib, as patients taking low-dose aspirin were excluded by the protocol from participation in the VIGOR trial. Hence, it is unclear whether concomitant therapy with low-dose aspirin completely blocks the beneficial effects of a COX-2 selective inhibitor. It is prudent, therefore, to consider concomitant therapy with a gastroprotective agent such as a proton pump inhibitor or miso-

prostil in patients who must receive both low-dose aspirin and a coxib if their risk of upper GI events is of sufficient magnitude. There is at present no evidence, based on results of experiments with rofecoxib, that COX-2 selective inhibitors interfere with the antiplatelet effects of low-dose aspirin, as these inhibitors do not enter the channel of the COX-1 enzyme to block the binding site of aspirin to the serine residue in position 529 [28].

Conclusion

It is apparent as we enter 2003 that the study of COX-2 selective inhibitors will remain an exciting and active area of basic and clinical research with an expected evolution and revision of evidence-based recommendations. The recent discovery of an alternative splice variant of COX-1 that is selectively inhibited by acetaminophen and potently inhibited by some nonselective NSAIDs may provide another pathway for development of additional agents for treatment of patients with arthritis [29]. Further large outcomes studies of COX-2 selective inhibitors in patients with arthritis and as cancer chemopreventive agents may produce additional informative data on the unresolved issues discussed above.

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