Commentary

COX-2: Where are we in 2003?

Distinction from NSAIDs becoming blurred

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Abstract

The distinction between cyclooxygenase-2-selective inhibitors (CSIs) and nonsteroidal anti-inflammatory drugs ultimately must be clinical and must be clinically and economically relevant. This distinction needs to be demonstrated in a substantial and clinically relevant difference in the respective rates of serious adverse reactions of the upper gastrointestinal tract. Event-driven, randomized, blinded, controlled trials with sufficient power are required to resolve uncertainties concerning the relative risk of thrombotic cardiovascular events in patients taking CSIs who have risk factors for these events. Patients and situations more representative of those in primary-care practice – elderly, comorbidities, comedication – need to be included in larger studies to provide a better understanding of the risks and benefits of CSIs.

Keywords: adverse reactions, aspirin hypersensitivity, concurrent gastroprotective agents, COX-2 selective inhibitors, thrombosis

Introduction

There are several key issues concerning cyclooxygenase-2 (COX-2)-selective inhibitors (CSIs) for 2003:

1. What exactly are CSIs and how are they differentiated from nonsteroidal anti-inflammatory drugs (NSAIDs)?
2. Is there a problem concerning the cardiovascular safety of CSIs?
3. What is the clinical approach to coprescribing low-dose aspirin and CSIs?
4. What is the merit, if any, of coprescription of gastroprotective agents such as proton-pump inhibitors in patients at high risk of upper gastrointestinal adverse effect from anti-inflammatory drugs including CSIs?
5. Are CSIs safe in patients with aspirin sensitivity?

What do we mean by 'COX-2-selective inhibition' and does this term have clinical significance?

We now have second-generation CSIs: valdecoxib, parecoxib, lumiracoxib and etoricoxib. However, there are unresolved issues with this class of drug.

Defining a CSI has become increasingly difficult. Some NSAIDs of characteristic weak acidic chemical nature, such as diclofenac and meloxicam, display some degree of 'selectivity' for inhibition of human COX-2 in comparison with COX-1, as has been shown in appropriate whole-blood-based *in vitro* assay systems [1,2], and yet diclofenac is labelled an NSAID and meloxicam a CSI. There are anti-inflammatory drugs that have a reputation largely based on spontaneous reports, case–control or cohort studies, or small, short, randomized, controlled studies for lower rates of upper gastrointestinal toxicity. Included in this category are drugs such as etodolac, nimuleside and nabumetone, which also appear to display some degree of 'selectivity' for COX-2. This problem of classification and differentiation between CSI and NSAID is confusing and affects prescribing decisions. It seems to revolve around the following issues:

1. Whether the drug was deliberately designed to inhibit the COX-2 isoenzyme using the identified structure of the enzyme and its differentiation from the structure of COX-1. This contrasts with the situation of COX-2

 CI = confidence interval; COX-2 = cyclooxygenase-2; CSI = COX-2-selective inhibitor; NSAID = nonsteroidal anti-inflammatory drug.

selectivity being demonstrated for an NSAID that was synthesized before knowledge of the structure of COX-2 (for example, diclofenac and meloxicam were not designed to specifically inhibit COX-2, whereas celecoxib and rofecoxib were).

2. The degree of rigour in testing the hypothesis that a purported CSI is markedly superior to conventional, dual inhibitors of COX-1 and COX-2 in respect of upper gastrointestinal toxicity. Rofecoxib and celecoxib have been subject to much sterner tests of relative gastrointestinal safety than other NSAIDs; these tests include endoscopic and outcome studies using very high dose rates relative to clinically recommended doses, long durations of exposure to drugs during these tests and substantial numbers of patients [3–5].
3. Some agencies, with the remit of determining the quality of the 'evidence base' behind claims of superiority and incremental cost–benefit, perhaps undervaluing some issues of study design: duration, number of subjects, and doses of drugs used.

As we have learned painfully in other areas of therapeutics, the proper test of a drug is in demonstrated health outcomes of value. Reduction of the serious morbidity and mortality accruing from adverse effects of NSAIDs on the upper gastrointestinal tract has been an appropriate target for improvement for many years. Largely on the basis of the VIGOR study [3], the FDA has approved an alteration to the rofecoxib label indicating that it is safer for the gastrointestinal tract than are conventional NSAIDs. This study, in over 8000 patients with rheumatoid arthritis, showed a 50–60% reduction in the rate of confirmed, clinically important upper gastrointestinal events, namely perforation, obstruction, symptomatic peptic ulceration and serious upper gastrointestinal bleeding. This contrast was demonstrated at a dose of rofecoxib twice that recommended for the treatment of rheumatoid arthritis (50 mg daily), the patients being followed for a median of 9 months, in comparison with a full anti-inflammatory dose of naproxen (1500 mg daily) [3]. Expressed another way, there were 2.09 versus 4.49 events per 100 patient years of therapy in rofecoxib and naproxen, respectively, which is a highly significant difference. Even though double the upper recommended dose of rofecoxib was used, this finding translates to 41 patients needing to be treated with rofecoxib (50 mg/day) to avoid one clinically significant upper gastrointestinal event per annum versus naproxen (1500 mg/day).

A similar alteration to the celecoxib label has not been allowed by the FDA, because of various problems surrounding the design, analysis, and publication of the CLASS study and the FDA analysis of the complete data from the study [4,5]. Subsequent studies increasingly indicate that celecoxib has a significant gastrointestinal advantage over conventional NSAIDs, as would be expected on the basis of extensive endoscopy studies [6,7]. However, in patients at very high risk of recurrent bleeding, celecoxib (200 mg twice daily) did not protect better than diclofenac (150 mg daily) plus omeprazole (20 mg daily), the risk of rebleeding being 4.9% for celecoxib (confidence interval [CI] 3.1–6.7) versus 6.4 for diclofenac plus omeprazole (CI 4.3–8.4), suggesting substantial room for improvement in this group of patients [8].

There is a continuum from the NSAIDs that are relatively selective for COX-1, to those that are 'dual inhibitors' of COX-1 and COX-2, on to those that show increasing relative selectivity for COX-2, and ending in those drugs, such as rofecoxib and the second-generation COX-2 inhibitors such as etoricoxib, that are highly selective for COX-2 [2]. This designation needs to be undertaken fairly and rigorously, using appropriate whole-blood-based *in vitro* systems [1,2,9]. In order to deal with the increasing confusion generated by claims of selectivity, the resultant ratio is best regarded as a surrogate indicator only. The designation 'CSI' should indicate a drug that not only shows substantial selectivity *in vitro* and preferably *ex vivo* using the whole blood assays for COX-1 and -2, but also substantial differentiation from conventional NSAIDs with respect to upper gastrointestinal damage in reasonably long studies of endoscopic and gastrointestinal outcomes. Most importantly, differentiation should be demonstrated at drug doses of at least the maximum recommended, or well above those expected to be used to control inflammation [5]. With this approach, clinicians could have confidence that the label CSI translates into a drug with a definite advantage in gastrointestinal safety across the whole dosage spectrum. Unfortunately, such clarity does not exist today.

Cardiovascular safety

Concern continues regarding the cardiovascular safety of highly selective CSIs, because of the unexpected but significantly higher rate of cardiovascular thrombotic events with rofecoxib than with naproxen seen only in the VIGOR study [10]. The theoretical rationale for concern has been boosted by the work of Cheng and colleagues using knock-out animals, who showed that not only is endothelial COX-2-derived prostacyclin inhibited by CSIs, but also its relative reduction by CSIs results in a 'disinhibition' of thromboxane production from platelets [11]. Thromboxane A_2 unopposed by prostacyclin in individuals with increased risks of cardiovascular thrombosis is a concern with enough evidence to be reflected in an FDA-mandated recent label change for rofecoxib. Furthermore, case reports indicate that patients with thrombophilic conditions are at risk from CSIs, and the labels for both rofecoxib and celecoxib reflect this.

Increasing comfort has been taken from large-scale meta-analyses of clinical trials programmes of celecoxib and rofecoxib [12–14]. Thus, a recent review of the clinical

trial database for rofecoxib in over 28,000 patients concluded that rofecoxib was not different from non-naproxen NSAIDs but that naproxen might be providing cardiovascular protection, at least in rheumatoid arthritis. However, as noted, the FDA has added a description of the cardiovascular findings in the VIGOR study to the label for rofecoxib along with a statement urging "caution in patients with a medical history of ischaemic heart disease…" [15]. Meanwhile, it has become apparent that chronic inflammation as seen in rheumatoid arthritis is an important risk factor for thrombotic cardiovascular adverse events, delivering a relative risk of the order of 2.

Resolution of this important issue of safety of CSIs in individuals with various degrees of risk for thrombotic events requires large-scale, event-driven, randomized, controlled trials versus conventional NSAIDs in patients with known background cardiovascular risk factors. These studies need to be undertaken in patients properly managed with respect to their cardiovascular risk with appropriate antiplatelet therapy. Also, careful consideration needs to be given to the exclusion criteria, in order to assure that a lower-risk population is not studied. The second-generation CSIs such as etoricoxib and valdecoxib, which are more selective for COX-2 than first-generation CSIs [16], should be able to inform us properly about the cardiovascular risks of highly selective inhibition of COX-2 versus COX-1.

COX-2-selective inhibitors and concomitant low-dose aspirin

A surprising finding from the CLASS study was that in the 21% of patients taking prophylactic low doses of aspirin, the relative protection from serious upper gastrointestinal bleeding and perforation versus the NSAIDs ibuprofen and diclofenac was lost [4]. Aspirin, even in low, prophylactic cardiovascular doses, is known to increase the risk of serious bleeding from the upper gastrointestinal tract 2-to 4-fold [17]. However, it is also well known that there is a dose response for NSAIDs and the risk of serious upper gastrointestinal bleeding [18,19]. One would expect that aspirin plus an NSAID would lead to more serious upper gastrointestinal adverse effects than aspirin plus a CSI and that the rate for aspirin plus a CSI would be similar to that expected from aspirin alone. Indeed, Weil *et al.* demonstrated a relative risk of 3.3 for aspirin alone (CI 2.5–4.4), of 4.9 for NSAIDs alone (CI 3.9–6.1) and of 7.7 for aspirin plus NSAID (CI 3.6–16.4); however, the study suffered obviously from lack of power [17]. Therefore, one would expect aspirin plus a CSI to be associated with less bleeding than aspirin plus an NSAID. A number of subsequent studies have suggested that this may be the case [6,7], in contrast to the unexpected findings in the CLASS study.

Again, definitive studies based on clinically important gastrointestinal outcomes are required to resolve this issue. Until such studies have been done, individuals with identified cardiovascular risk factors requiring platelet inhibitory therapy should get it. As our estimation of the risk of upper gastrointestinal haemorrhage increases, then it is reasonable that our inclination to use a CSI instead of an NSAID should increase. Importantly, there are no data to show that in this clinical situation celecoxib or rofecoxib, unlike ibuprofen, blocks the actions of aspirin on the platelet [20].

Coprescription of gastroprotective agents

As the risk for gastrointestinal bleeding and perforation increases in patients, and in situations where treatment with an anti-inflammatory analgesic drug would be helpful, prescribers are increasingly coprescribing gastroprotective agents. This is logical if we extrapolate from the pivotal studies indicating a protective effect for proton-pump inhibitors when NSAIDs are used [21]. The question of whether these drugs add to the protective effect of the CSIs remains moot but is worthy of elucidation for the proportion of patients for whom such an approach might be reasonable.

COX-2-selective inhibitors in patients with hypersensitivity to aspirin?

A number of studies now confirm that the CSIs rofecoxib and celecoxib are very much less likely than conventional NSAIDs to be associated with hypersensitivity reactions in patients with known hypersensitivity to aspirin [22–24]. However, because of the heterogeneity of the aspirin hypersensitivity syndrome, great caution still needs to be taken if prescribing CSIs in this situation. Cases of angioedema have been reported [25]. Use of the most selective members of the CSI class would seem wise.

Conclusion

The CSIs have been the source of great interest and advance in rheumatology. A clearer picture of the clinical relevance of the CSIs in contrast to NSAIDs is emerging. The risk of thrombotic cardiovascular events with CSIs in patients with risk factors for thrombotic events needs further elucidation. Uncertainties concerning the use of CSIs concomitant with gastroprotective agents in patients taking low doses of aspirin prophylactically and in patients with a history of aspirin hypersensitivity need resolution. The emergence of the CSIs has led to rheumatology becoming more closely intertwined with cardiovascular medicine. Also, methodologies of clinical trials have advanced significantly as a consequence of the introduction of CSIs. However, there is much more to be revealed in 2003.

Competing interests

The author is an advisory board member (Merck Sharpe & Dohme) and a clinical investigator for rofecoxib and etoricoxib. He has also served as an advisory board member for celecoxib and been an investigator for that drug.

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