Commentary

Cyclooxygenase-2: where are we in 2003?

Cardiovascular risk and COX-2 inhibitors

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Received: 25 September 2002 Revisions received: 3 October 2002 Accepted: 4 October 2002 Published: 28 October 2002

Arthritis Res Ther 2003, **5**:8-11 (DOI 10.1186/ar609)

Abstract

Selective cyclooxygenase-2 (COX-2) inhibitors were developed to reduce the gastrointestinal toxicity of conventional nonsteroidal anti-inflammatory agents. However, COX-2 inhibitors decrease prostacyclin production and may disrupt the normal homeostatic balance, leading to a prothrombotic state and offsetting the potential gastrointestinal benefits. Available clinical data and basic biological studies raise significant concern about the potential prothrombotic effect of this class of drugs. Two recent studies with a newer, more selective COX-2 inhibitor have added to the already existing concern about the cardiovascular safety of these agents. The widespread use of these agents mandates prospective, randomized evaluation of the cardiovascular safety of COX-2 inhibitors.

Keywords: cardiovascular risk, cyclooxygenase-2 inhibitors, prothrombotic effects, prostaglandins

Introduction

Aspirin and traditional nonsteroidal anti-inflammatory agents (NSAIDs) are effective analgesic and anti-inflammatory agents, but they also have significant gastrointestinal toxicity. The gastrointestinal toxicity of NSAIDs is apparently related to inhibition of the cyclooxygenase-1 (COX-1) isoform [1]. Following the discovery by Fu *et al*. of a novel COX protein in monocytes stimulated by interleukin [2], Kujubu *et al*. identified a gene with significant homology to COX-1 [3]. Identification of this cyclooxygenase-2 (COX-2) isoform resulted in the development of selective COX-2 inhibitors, with the hope of producing a safer analgesic and anti-inflammatory agent. The COX-2 inhibitors have generated rapid growth in the US anti-arthritic market, with total sales exceeding $4.7 billion in 2001 and a 28% growth in year over year sales [4].

The hypothesis of the safety of COX-2 inhibitors as anti-inflammatory agents is based on the premise that COX-1 predominates in the stomach, yielding protective prostaglandins, while COX-2 is induced in inflammation giving rise to pain, swelling and discomfort. It has now been unequivocally demonstrated, however, that selective COX-2 inhibitors also decrease vascular prostacyclin (PGI_2) production and may affect the homeostatic balance, leading to a prothrombotic state [5]. By decreasing vasodilatory and antiplatelet aggregatory PGI_2 production, COX-2 inhibitors may tip the balance in favor of prothrombotic eicosanoids (thromboxane A_2 [TXA_2]) and may lead to increased cardiovascular thrombotic events [6].

Preclinical/molecular studies

Several basic research studies have demonstrated beneficial cardiac effects of the COX-2 enzyme and potential harmful effects of COX-2 inhibitors. Shinmura *et al*. demonstrated that COX-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning [7]. By examining the late phase of ischemic preconditioning in rabbits, they demonstrated that ischemic preconditioning resulted in a rapid increase in myocardial COX-2 mRNA levels. This was followed by an increase in COX-2 protein expression and in the myocardial content of prostaglandin E_2 and 6-keto-PGF(1α) [7]. Administration of two unrelated COX-2 selective inhibitors (NS-398 and

COX-1 = cyclooxygenase-1; COX-2 = cyclooxygenase-2; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory agent; PGI_2 = prostacyclin; TXA_2 = thromboxane A_2.

celecoxib) 24 hours after ischemic preconditioning abolished the ischemic preconditioning-induced increase in tissue levels of prostaglandin E_2 and 6-keto-PGF(1α). The same doses of NS-398 and celecoxib, given 24 hours after ischemic preconditioning, completely blocked the cardioprotective effects of late preconditioning against both myocardial stunning and myocardial infarction (MI), indicating that COX-2 activity is necessary for ischemic preconditioning to occur. These results demonstrate that upregulation of COX-2 plays an essential role in the cardioprotection afforded by the late phase of ischemic preconditioning [7].

Hennan *et al*. demonstrated the important role of COX-2 in the homeostatic balance by showing that the increase in time to vascular occlusion with aspirin in a canine coronary thrombosis model was abolished with a selective COX-2 inhibitor, celecoxib [8]. In their study of canine circumflex coronary artery thrombosis, oral high-dose aspirin produced a significant increase in time to arterial occlusion. This observed increase in time to occlusion was abolished when celecoxib was coadministered to animals dosed with aspirin. The study of Hennan *et al*. also suggests the important role of COX-2-derived PGI_2, and it raises concerns regarding an increased risk of acute vascular thrombotic events in patients receiving COX-2 inhibitors [8].

Other beneficial effects of COX-2 have also been demonstrated in the heart. Dowd *et al*. demonstrated that inhibition of COX-2 aggravates doxorubicin-mediated cardiac injury *in vivo* [9]. Doxorubicin induces COX-2 activity in rat neonatal cardiomyocytes, and this expression of COX-2 limits doxorubicin-induced cardiac cell injury. Doxorubicin-increased cardiac injury was aggravated by coadministration of SC236 (a COX-2 inhibitor) but not of SC560 (a COX-1 inhibitor).

Cheng *et al.* [10] recently used an elegant transgenic knockout mice model to further elucidate the important physiological role of COX-2 enzyme in vascular homeostasis. The investigators studied deletions of the prostaglandin receptor to understand the effects of COX-2 inhibitors *in vivo*. Mice with an absent prostaglandin receptor (IPKO) should mimic the clinical effect of taking COX-2 agents, as these drugs would inhibit prostaglandin production without affecting TXA_2. The COX-2 knockout resulted in an enhanced proliferative response to injury and in a significant increase in TXA_2 biosynthesis. These results suggest that PGI_2 may modulate the platelet–vascular interactions *in vivo*, and that PGI_2 may have a beneficial effect by specifically limiting the prothrombotic response to TXA_2. These well-designed, *in vivo* gene knockout studies raise further significant concern about the prothrombotic effects and cardiovascular safety of COX-2 inhibitors.

Clinical studies

Notably, clinical data with COX-2 inhibitors have also raised concerns about cardiovascular safety [11]. There have been two major multicenter trials with these agents, and several smaller studies.

The Vioxx Gastrointestinal Outcomes Research Study trial, a double-blind, randomized, stratified, parallel group study of 8076 patients, compared the gastrointestinal toxicity of 50 mg rofecoxib daily or 1000 mg naproxen daily during chronic treatment for patients with rheumatoid arthritis [12]. Aspirin use was not permitted in the study. The results of the event-free survival analysis showed that the relative risk of developing a cardiovascular event in the rofecoxib treatment arm was 2.37 (95% confidence interval = 1.39–4.06, $P = 0.0016$) [13].

The Celecoxib Arthritis Safety Study was a double-blind, randomized, controlled trial of 8059 patients. These participants were randomized to receive either 400 mg celecoxib twice per day, 800 mg ibuprofen three times per day or 75 mg diclofenac twice per day [14]. Aspirin use (<325 mg/day) was permitted in this study. The Celecoxib Arthritis Safety Study trial with celecoxib demonstrated no statistically significant difference in cardiovascular events as compared with the NSAIDs. However, there was a numerical excess of MI events in the celecoxib group, regardless of whether patients were concurrently taking aspirin. Since the trial was not powered to detect an increase in MI, one cannot conclude that celecoxib is exempt from prothrombotic events, especially with the trend for more MIs.

A combined analysis of 23 phase IIb–phase V rofecoxib studies demonstrated no evidence for an excess of cardiovascular events for rofecoxib relative to either placebo or the non-naproxen NSAIDs that were studied [15]. Konstam *et al*., employees of the manufacturer of rofecoxib, concluded that differences observed between rofecoxib and naproxen were the result of the antiplatelet effects of naproxen. A large cohort study by Ray *et al.* [16], however, demonstrated that there was no protective effect of naproxen on the risk of coronary heart disease (rate ratio = 0.95, 95% confidence interval = 0.82–1.09). Other major limitations of the analysis by Konstam *et al.* [15] include combining heterogeneous patient populations receiving different dosages of the COX-2 agents. Not a single study has considered patients with coronary heart disease or was designed to assess cardiovascular safety.

A second-generation, even more selective COX-2 agent, etoricoxib, has more recently been tested in two trials [17,18]. Although identical in design and drug dosages, and very similar in size, the trials reported discordant findings. The study by Collantes *et al.* [18] demonstrated no

difference in efficacy between etoricoxib and naproxen in treating patients with rheumatoid arthritis, while the study by Matsumoto *et al*. demonstrated etoricoxib to be significantly more effective [17]. More importantly, despite excluding patients with a history of cardiovascular disease in the form of angina, congestive heart failure, history of MI, coronary angioplasty, coronary bypass, stroke and transient ischemic attacks, there were two adjudicated cardiovascular events out of 323 patients in the Matsumoto *et al*. study [17], and two events out of 353 patients in the study by Collantes *et al.* [18]. A recent analysis by Ray *et al*. of individuals on the Tennessee Medicaid Program demonstrated that users of high dose rofecoxib were 1.70 (95% confidence interval 0.98–2.95, $P = 0.058$) times more likely than non users to have coronary artery disease [19].

Conclusions

Seminal experimental studies, including those with knockout mice, have demonstrated that the COX-2 isoform produces vascular PGI_2, which is a pivotal biologic vasodilator and an inhibitor of platelet aggregation. Selective COX-2 inhibitors have no effect on TXA_2 production but, by decreasing PGI_2 production, they may affect the homeostatic balance between prothrombotic TXA_2 and antithrombotic PGI_2, and may lead to an increase in thrombotic cardiovascular events [20,21].

Given the results of several large clinical trials of COX-2 inhibitors, it is clear that the theoretical concern for a prothrombotic effect is now transformed to a clinical reality. The apparent hazard does not appear to be large and, in absolute terms, may be a fraction of 1% excess and may be confined to patients with an as yet undefined, specific genetic susceptibility. With such an exceptionally large patient population at risk, however, it is imperative to determine the precise extent of the risk and the methods to avoid risk. In patients with atherosclerotic heart disease, the use of low-dose aspirin in conjunction with a COX-2 inhibitor is one possible way to mitigate the risk. However, the data from the experimental celecoxib study performed with aspirin [8] and the clinical trial allowing aspirin [14] have failed to offer reassurance. Furthermore, the risk of gastrointestinal bleeding is expected to be heightened with concurrent use of aspirin and COX-2 inhibition such that any clinical advantage over a NSAID could be lost.

The importance of the public health issue cannot be overstated. The class of drugs have yet to be assessed in a single trial of patients with known atherosclerotic disease, who stand to be at the highest risk of adverse events. The population of patients taking COX-2 inhibitors includes tens of millions of individuals with such concomitant underlying disease. Ironically, the manufacturers of the first-generation COX-2 inhibitors spent over $265 million in 2001 for direct-to-consumer advertising to promote their drugs [22], but have failed to conduct a prospective trial of COX-2 inhibitors in patients with cardiovascular disease. We will not have advanced in any meaningful way in 2003 unless such a trial is undertaken.

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