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Commentary

Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events

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Abstract

Selective cyclooxygenase-2 (COX-2) inhibitors were developed as a response to the gastrointestinal toxicity of conventional nonsteroidal anti-inflammatory agents (NSAIDs). However, COX-2 inhibitors decrease vascular prostacyclin (PGI_2) production and may disrupt the homeostatic mechanisms that limit the effects of platelet activation. Basic and clinical data raise concerns about a potential prothrombotic effect of this class of drugs. The widespread popularity of these agents mandates their prospective evaluation in patients with cardiovascular diseases or who are at risk for cardiovascular events.

Keywords: COX-2 inhibitors; Prothrombotic effects; Prostaglandins; Rofecoxib; Celecoxib; Cardiovascular risk

1. Introduction

NSAIDs have proven analgesic, anti-inflammatory, and antithrombotic properties, but also have significant gastrointestinal toxicity. The gastrointestinal toxicity appears to be related to COX-1 inhibition [1]. In 1990, Fu *et al.* [2] detected a novel COX protein in monocytes stimulated by interleukin, and a year later Kujubu *et al.* [3] identified a gene with considerable homology to COX-1. Identification of this COX-2 protein rekindled the efforts of the pharmaceutical industry to produce a safer analgesic, anti-inflammatory drug via selective inhibition of COX-2, and this class of drugs was introduced in 1999. The COX-2 inhibitors generated rapid growth in the US antiarthritic market in 2000, with total sales exceeding $6 billion, and the volume of prescriptions reaching 121.3 million [4].

The development of COX-2 inhibitors as anti-inflammatory agents without gastric toxicity is based on the fact that COX-1 predominates in the stomach, yielding protective prostaglandins, while COX-2 is induced in inflammation, giving rise to pain, swelling, and discomfort. However, selective COX-2 inhibitors also decrease vascular PGI_2 production and may affect the balance between prothrombotic and antithrombotic eicosanoids [5]. Unlike the platelet inhibition afforded by COX-1 inhibitors, COX-2 inhibitors do not share this beneficial antithrombotic property. In contrast, by decreasing vasodilatory and anti-aggregatory PGI_2 production, COX-2 inhibitors may tip the balance in favor of prothrombotic eicosanoids (thromboxane A_2) and may lead to increased cardiovascular thrombotic events [6]. However, atherosclerosis is a process with inflammatory features [7], and selective COX-2 inhibitors may potentially have anti-atherogenic effects by virtue of inhibiting inflammation.

2. Available data

2.1. Animal data

Several basic research studies point to a cardioprotective effect of COX-2 and the potential detriment of COX-2 inhibitors. Shinmura *et al.* [8] demonstrated that COX-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning. The authors examined the role of COX-2 in the late phase of ischemic preconditioning in a total of 176 conscious rabbits. Ischemic preconditioning (six cycles of 4 min coronary occlusions/4 min reperfusions) resulted in a rapid increase in myocardial COX-2 mRNA levels followed 24 hr later by an increase in COX-2

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Abbreviations: NSAIDs, nonsteroidal anti-inflammatory agents; COX, cyclooxygenase; PGI_2, prostacyclin; VIGOR, Vioxx Gastrointestinal Outcomes Research Study; CLASS, Celecoxib Long-Term Arthritis Safety Study; AERS, Adverse Event Reporting System.

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protein expression and in the myocardial content of prostaglandin E_2 (PGE_2) and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$). Administration of two unrelated COX-2 selective inhibitors (NS-398 and celecoxib) 24 hr after ischemic preconditioning abolished the ischemic preconditioning-induced increase in tissue levels of PGE_2 and 6-keto-$PGF_{1\alpha}$. The same doses of NS-398 and celecoxib, given 24 hr after ischemic preconditioning, completely blocked the cardioprotective effects of late preconditioning against both myocardial stunning and myocardial infarction, indicating that COX-2 activity is necessary for this phenomenon to occur. These results demonstrate that, in rabbits, up-regulation of COX-2 plays an essential role in the cardioprotection afforded by the late phase of ischemic preconditioning. Therefore, this study identified COX-2 as a cardioprotective protein [8]. Hennan *et al.* [9] recently demonstrated that the observed increase in time to occlusion with aspirin in a canine coronary thrombosis model was abolished with celecoxib. In this study, circumflex coronary artery thrombosis was induced in dogs by electrolytic injury. Oral high-dose aspirin with an endothelial recovery period produced a significant increase in time to vessel occlusion. The observed increase in time to occlusion was abolished when celecoxib was administered to animals dosed with aspirin. The vasomotor effect of endothelium-derived PGI_2 was also examined by monitoring coronary flow during intracoronary administration of arachidonic acid or acetylcholine. In celecoxib-treated animals, vasodilation in response to arachidonic acid was reduced significantly compared with controls. The results of this study indicated important physiological roles for COX-2-derived PGI_2 and raise concerns regarding an increased risk of acute vascular events in patients receiving COX-2 inhibitors [9]. Other salutary effects of COX-2 have also been demonstrated in the heart. Dowd *et al.* [10] recently demonstrated that inhibition of COX-2 aggravates doxorubicin-mediated cardiac injury *in vivo*, suggesting potential salutary effects of COX-2 in the heart. 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, detected as a rise in plasma cardiac troponin T and serum lactate dehydrogenase, and cardiomyocyte apoptosis was aggravated by the coadministration of SC236 (a COX-2 inhibitor) but not SC560 (a COX-1 inhibitor). These data further support the beneficial effects of COX-2 in the heart.

2.2. Clinical data

The available clinical data with COX-2 inhibitors pertaining to cardiovascular endpoints were summarized recently [11]. There have been two major, multicenter trials with these agents and two smaller studies. The Vioxx Gastrointestinal Outcomes Research Study (VIGOR) trial was a double-blind, randomized, stratified, parallel group study of 8076 patients to compare the occurrence of gastrointestinal toxicity of rofecoxib (50 mg daily) or naproxen (1000 mg daily) during chronic treatment for patients with rheumatoid arthritis [12]. Aspirin use was not permitted in the study. The baseline characteristics between the treatment groups in the VIGOR trial demonstrated no meaningful or significant differences. Ninety-eight cases (65/4047 from rofecoxib and 33/4029 from naproxen) were sent for adjudication of vascular events. Of these, 46 patients in the rofecoxib group and 20 in the naproxen group were adjudicated to have had serious thrombotic cardiovascular events. The results of the event-free survival analysis on the 66 cases showed that the relative risk of developing a cardiovascular event in the rofecoxib treatment arm was 2.37 (1.39–4.06), $P = 0.0016$ [13]. A subgroup analysis was performed for ''aspirin-indicated'' and ''aspirin-not-indicated'' patients in the VIGOR trial. In this trial, aspirin-indicated patients were defined as subjects with a past medical history of stroke, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions. Only 321 (3.9%) patients were aspirin-indicated patients (170 in rofecoxib and 151 in naproxen), as need for aspirin was an exclusion criterion. The relative risk ratio of developing serious cardiovascular events in aspirin-indicated patients between rofecoxib and naproxen was 4.89 (1.41–16.88), $P = 0.012$, and the relative risk for aspirin-not-indicated patients was 1.89 (1.03–3.45), $P = 0.04$ [13].

The Celecoxib Long-Term Arthritis Safety Study (CLASS) was a double-blind, randomized controlled trial of 8059 patients, in which patients received celecoxib (400 mg twice per day), ibuprofen (800 mg three times per day), or diclofenac (75 mg twice per day) [14]. Aspirin use (<325 mg per day) was permitted in this study. The CLASS trial with celecoxib demonstrated no significant difference in cardiovascular events as compared with the NSAIDs.

Studies 085 and 090, although not published, were reported to the FDA. Study 085, which tested the efficacy and safety of rofecoxib versus nabumetone, had a sample size of 1042 patients and allowed use of low-dose aspirin for the prevention of ischemic events [13]. There were three total cardiovascular events in this trial with one event with rofecoxib (0.2%) as compared with 2 (0.4%) in the nabumetone group and 0 (0%) in the placebo group. Study 090, with a similar design as study 085, reported a total of six serious cardiovascular events with rofecoxib (1.5%) as compared with 2 (0.5%) in the nabumetone group and 1 (0.5%) in the placebo group [13].

An Adverse Event Reporting System (AERS) search by the FDA revealed 144 unduplicated thrombotic or embolic cases for celecoxib and 159 cases for rofecoxib. Forty-two celecoxib cases and 60 rofecoxib cases were excluded for either lack of documented event, hemorrhagic strokes in which prothrombin time (PT), partial thromboplastin time

(PTT), or the International Normalized Ratio (INR) were above the normal range, or second-hand reports with no confirmed diagnosis. Ninety-nine thrombotic or embolic events were attributed to rofecoxib and 102 cases to celecoxib [15].

3. Limitations of available clinical data

There are several limitations of the currently available clinical data. The increase in cardiovascular events in these trials was unexpected, and evaluation of these endpoints was not pre-specified. There remains considerable uncertainty in any post-hoc analysis. The patient populations in these trials were relatively healthy, without multiple cardiac risk factors. The low cardiovascular risk of the population studied and the short follow-up in the trials to date may significantly underestimate the magnitude of the hazard. Also, the trials examined only addressed continuous use of COX-2 inhibitors. Currently, no data exist on cardiovascular safety for the sporadic, intermittent use of these agents by individuals for musculoskeletal pain, which appears to be the most frequent pattern of use. There are also major differences in the patient population studied in the different trials. Patients with rheumatoid arthritis are known to have higher risk for cardiovascular events and might have contributed to increased events in the VIGOR trial. However, if one accepts that patients with rheumatoid arthritis are at increased risk for events, one is still faced with the difference in cardiovascular events between rofecoxib and naproxen. One could then extend this argument that any patient with other cardiac risk factors remains at risk with these agents. There are also significant differences in the nature of the NSAIDs studied in the different trials, which may also have affected the outcomes.

4. Comments

Aspirin and NSAIDs interfere with prostaglandin synthesis by inhibiting COX, the key to both their therapeutic and toxic effects. The COX-1 isoform is constitutively expressed in most cells, which results in the production of homeostatic prostaglandins that maintain gastrointestinal mucosal integrity as well as renal blood flow. It is also expressed in platelets and mediates production of thromboxane A_2, a potent platelet activator and aggregator. The COX-2 isoform produces prostaglandins at inflammatory sites as well as PGI_2, which is a vasodilator and inhibitor of platelet aggregation. Selective COX-2 inhibitors would have no effect on thromboxane A_2 production, but by decreasing PGI_2 production may tip the natural balance between prothrombotic thromboxane A_2 and antithrombotic PGI_2, and may lead to an increase in thrombotic cardiovascular events [16,17].

The VIGOR trial demonstrated a significantly increased risk of cardiovascular event rates with the use of rofecoxib despite the fact that the study enrolled patients who did not require aspirin for protection from ischemic events. Patients with angina, congestive heart failure, myocardial infarction, coronary artery bypass surgery within 1 year, stroke or transient ischemic attacks within 2 years, and uncontrolled hypertension were excluded from this trial. However, these criteria can be viewed as stringent, given data from trials that support more liberal use of aspirin for primary prevention.

The results of the VIGOR trial can be explained by two alternative hypotheses, either a significant prothrombotic effect of rofecoxib or an antithrombotic effect of naproxen (or conceivably both). There is clinical evidence that flurbiprofen (50 mg twice daily for 6 months) reduced the incidence of myocardial infarction by 70% compared with a placebo [18]. Indobufen, another NSAID, was as effective as aspirin in preventing saphenous vein graft occlusion after bypass surgery [19]. Because of the evidence for an antiplatelet effect of naproxen, it is difficult to assess whether the difference in the cardiovascular event rates in VIGOR was due to a benefit from naproxen or a prothrombotic effect of rofecoxib. As opposed to the VIGOR trial, the CLASS trial with celecoxib did not show a significant increase in cardiovascular event rates as compared with NSAIDs. One explanation is the use of low-dose aspirin in the CLASS trial, and another is pharmacological differences in the NSAID agents used as a control in the two studies. Diclofenac and ibuprofen have significantly fewer antiplatelet effects as compared with naproxen. To have a vascular protective effect, near-complete inhibition of thromboxane over time is needed [20], and the degree of thromboxane inhibition with diclofenac and ibuprofen may not afford any cardioprotection. Furthermore, diclofenac exhibits a greater effect on PGI_2 inhibition than naproxen. Van Hecken *et al.* [21] demonstrated that diclofenac causes 94% inhibition of COX-2 as compared with 71% for naproxen. Thus, diclofenac has not only fewer antiplatelet effects, but may have some intrinsic prothrombotic effect among NSAIDs due to inhibition of vasodilatory PGI_2, and this may have masked the increase in event rates with celecoxib. Based upon available basic and clinical data, both rofecoxib and celecoxib appear potentially prothrombotic, and there exists no solid scientific hypothesis that would suggest a more favorable cardiovascular safety profile for either agent.

Two smaller studies (Protocols 085 and 090) with rofecoxib, which allowed the use of low-dose aspirin, did not demonstrate the significant increase in cardiovascular event rate as was noted in VIGOR. However, these studies had a smaller sample size and used 25% of the dose of rofecoxib as compared with VIGOR. Thus, the prothrombotic effect seen with rofecoxib may potentially be dose-dependent. Also, use of low-dose aspirin in these protocols may negate some of the gastrointestinal benefits

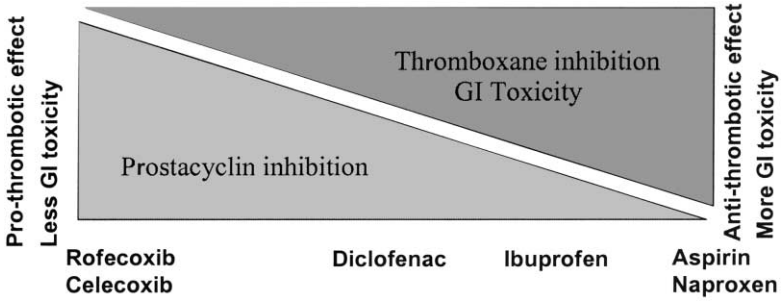

Fig. 1. Spectrum of biological activity of currently available nonsteroidal anti-inflammatory drugs. Each agent has a potentially different effect on thromboxane and PGI_2 synthesis (GI: gastrointestinal).

of selective COX-2 inhibition. There is evidence in the literature that gastrointestinal bleeding from aspirin is not dose-related [22].

COX-2 inhibitors have also been shown to increase blood pressure [23], and more patients in the VIGOR trial developed hypertension with rofecoxib than naproxen. For rofecoxib, the mean increase in systolic blood pressure in the VIGOR trial was 4.6 mmHg and an increase of 1.7 mmHg in diastolic blood pressure. These changes were larger than that with naproxen (1.0 mmHg systolic, and 0.1 mmHg diastolic increase). Changes in blood pressure in the CLASS trial were not reported. However, a trial comparing rofecoxib and celecoxib demonstrated that patients receiving celecoxib experienced less edema and less destabilization of blood pressure control compared with those receiving rofecoxib [24]. Systolic blood pressure increased significantly in 17% of rofecoxib-treated patients compared with 11% of celecoxib-treated patients ($P = 0.032$) at any study time point [24]. Some of the differential effects on blood pressure may be related to COX-2 selectivity of these agents. The biochemical selectivity of rofecoxib for COX-2/COX-1 inhibition based on an IC_{50} ratio is 267 compared with 30 for celecoxib [25]. There is evidence that a reduction of 2 mmHg in diastolic blood pressure results in about 40% reduction in the rate of stroke and 25% reduction in the rate of myocardial infarction [26]. The Heart Outcomes Prevention Evaluation Study demonstrated a significant reduction in cardiovascular events with 3–4 mmHg reduction in blood pressure [27]. Moreover, a recent re-analysis of 20 years of blood pressure data from the Framingham Heart Study [28] suggests that the degree of benefit expected from a decrease in blood pressure may have been underestimated. Thus, the elevation in blood pressure reported with the use of COX-2 inhibitors may potentially play a significant role in adverse cardiovascular outcomes.

It is clinically useful to consider non-selective and selective COX inhibitors as possessing a spectrum of biological effects, favorable and unfavorable (Fig. 1). On one end of the spectrum, COX-2 inhibitors show less propensity for gastrointestinal toxicity, but greater prothrombotic potential. At the other end of the spectrum, aspirin and naproxen show greater potential for gastrointestinal toxicity, but have a cardioprotective effect. Other agents fall along intermediate points in this spectrum. Clinicians may want to consider these patterns of risk and benefit in selecting the most appropriate agent for individual patients.

Together the clinical and basic data raise several important questions: (a) Are COX-2 inhibitors prothrombotic? (b) Can low-dose aspirin use offset the potential thrombotic risk? (c) Does low-dose aspirin negate the gastrointestinal safety of COX-2 inhibitors? (d) Should COX-2 drugs be avoided in patients with coronary artery disease? (e) Should they be avoided in patients at high risk for coronary disease? (f) Do these agents have any potential beneficial effects on atherosclerosis because of their aÇnti-inflammatory effects? (g) Is it possible to develop an agent that will inhibit COX-2 at inflammatory sites without affecting vascular COX-2 and PGI_2 production? Available data have raised concern about the increase in cardiovascular event rates for the presently available COX-2 inhibitors. Definitive evidence of such an adverse effect will require a prospective randomized clinical trial. Given the remarkable high exposure and popularity of this new class of medications, we believe that it is mandatory to conduct such a trial. Until then, we urge clinicians to exercise caution in prescribing these agents to patients with coronary artery disease or at risk for cardiovascular morbidity.

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