Cardiovascular risk: Are all NSAIDs alike?

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications purchased over the counter to treat acute and chronic pain and inflammation associated with a range of medical conditions.¹ It is estimated that NSAIDs are prescribed to about 25% of Canadians for short-term use, but overall use is likely much higher with over-the-counter availability.² Like any medication, the benefits of NSAIDs should be considered in tandem with the potential adverse effects. Side effects range from the mild and common to the severe and infrequent: dyspepsia, gastric or duodenal ulceration, sodium retention and subsequent hypertension, as well as increased incidence of cardiovascular (CV) adverse events. It was the withdrawal of rofecoxib from the market that brought to light the CV risk of NSAIDs and, in fact, a black-box warning now exists in NSAID product monographs, advising caution when prescribing to patients with ischemic heart disease, cerebrovascular disease and/or congestive heart failure.³ This article focuses on the CV effects associated with NSAID use by reviewing the recent literature on this topic.

Mechanism of action

The main mechanism of the analgesic and antipyretic actions of NSAIDs appears to be prostaglandin biosynthesis inhibition.⁴ The cyclooxygenase (COX)-1 enzyme is responsible for the production of prostaglandins and thromboxane, which are involved in routine physiological functions such as gastroprotection, platelet aggregation and renal blood flow. COX-2 is induced by inflammatory mediators, local injury and cytokines. The prostaglandins produced by COX-2 contribute to pain and

fever but are also involved in renal function, tissue repair and reproduction. Both COX-1 and COX-2 play a role in homeostasis: prostacyclin (prostaglandin I₂) is produced via COX-2 of endothelial cells and has antithrombotic effects, and thromboxane is produced by COX-1 found in platelets and is prothrombotic.⁴ Low-dose acetylsalicylic acid (ASA) is standard therapy in patients with high CV risk; the cardioprotective effect is achieved through *irreversible* inhibition of thromboxane (95% suppression of COX-1 activity). This is in contrast to other nonselective NSAIDs, which are *reversible* inhibitors of thromboxane with a lower inhibition, ranging from 59% to 95%.⁵

The most common adverse effects of NSAIDs involve the gastrointestinal tract; therefore, the COX-2 selective inhibitors appear more appealing than the nonselective NSAIDs in that they have similar anti-inflammatory properties with less gastrointestinal toxicity.⁶ While NSAIDs are grouped by relative COX-2 selectivity, growing evidence suggests that mechanisms and clinical outcomes do not follow a uniform class effect. Following the APPROVe (Adenomatous Polyp PRevention On Vioxx) trial, which brought to light the increased risk of CV events with rofecoxib,⁷ there has been considerable debate regarding the CV safety of COX-2 selective inhibitors, as well as traditional nonselective NSAIDs.

The COX-2 selective inhibitors may increase the risk of thrombotic events primarily due to the imbalance caused by inhibition of COX-2-mediated prostacyclin production without inhibition of COX-1-mediated thromboxane production.^{2,8} Multiple mechanisms likely contribute to the CV risks associated with NSAIDs and include differences in endothelial

function, oxidative stress and renal effects such as volume retention and hypertension.⁸ Pharmacokinetics may also play a role, since medications with longer half-lives prescribed once daily or medications with shorter half-lives taken more than once daily may be more apt to interfere with the COX system than medications such as celecoxib, which has a short half-life but is often prescribed once daily.⁸

Cardiovascular risk—evidence from the recent literature

A literature search was performed in July 2011 using OVID MEDLINE, International Pharmaceutical Abstracts, Reactions Weekly, Cochrane Database of Systematic Reviews and an internal citation database of pharmacy journals (AskSam) to identify recent relevant studies and reviews examining the association of NSAIDs and CV risk. The following search terms (Medical Subject Headings and key words) were used: *NSAIDs, cyclooxygenase 2 inhibitors, cardiovascular diseases, heart diseases, vascular diseases, myocardial infarction, adverse effect and adverse drug reaction*. Studies solely examining NSAIDs not available on the Canadian market were not considered. Additional studies referenced in the original findings were further identified for review. Three systematic studies considered relevant by the reviewers, which examined multiple anti-inflammatory agents, were retrieved and are examined in detail.

1. CV risks of NSAIDs in patients after hospitalization for serious coronary heart disease

The question of CV safety is of particular importance for patients with existing serious coronary heart disease, as their baseline risk of CV events is increased.^{9,10} This retrospective cohort study examined 5 individual NSAIDs (naproxen, ibuprofen, diclofenac, celecoxib and rofecoxib) in 48,556 patients (40–89 years old) recently hospitalized for myocardial infarction (MI), revascularization or unstable angina pectoris.⁹ The follow-up began 45 days postadmission, so results cannot be generalized to the early postdischarge period. The primary end point was serious coronary heart disease (acute MI or out-of-hospital death from coronary heart disease). Secondary end points were a composite of serious CV disease (nonfatal MI or stroke)

and death from any cause. For naproxen, the incidence rate ratio (IRR) relative to nonusers of any NSAID was 0.88 (95% confidence interval [CI], 0.66–1.17) for the primary end point and 0.91 (95% CI, 0.78–1.06) for the secondary end points, which were both lower than the rates of the other NSAIDs studied. When duration of use was taken into account, an increased risk of serious coronary heart disease was associated with short-term use (<90 days) of ibuprofen (IRR, 1.67; 95% CI, 1.09–2.57), diclofenac (IRR, 1.86; 95% CI, 1.18–2.92), rofecoxib (IRR, 1.46; 95% CI, 1.03–2.07) and celecoxib (IRR, 1.37; 95% CI, 0.96–1.94, nonsignificant), unlike naproxen (IRR, 0.88; 95% CI, 0.5–1.55). Longer duration of use, however, did not result in a significant increase in CV risk. The most commonly prescribed dose of naproxen was 1000 mg/d or greater, and there was no evidence of increased CV risk at these higher doses.

These results are somewhat in conflict with what was previously suggested by the APPROVE trial, in which the CV risk was not increased when NSAIDs were used for less than 18 months.⁷ Similarly, the VICTOR (Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime) trial demonstrated an increased risk after only 7.4 months of rofecoxib use.¹¹

2. An evidence-based review of the CV risks of NSAIDs

This review suggests that 5 key variables affect the extent of CV risk associated with NSAIDs: 1) COX-2 selectivity, 2) dose responsiveness, 3) plasma half-life, 4) blood pressure and 5) interaction with ASA.⁶ After reviewing key clinical trials, observational studies, systematic reviews and meta-analyses, the authors concluded that naproxen has consistently demonstrated lower risk compared with other nonselective and COX-2 selective NSAIDs. Diclofenac has generally been associated with the highest CV risk among nonselective NSAIDs. Evidence for celecoxib suggests an increased risk of CV events, especially at higher doses (800 mg/d), but also twice-daily regimens (200 mg twice daily). Available data on platelet effects suggest no reduction in cardioprotection when ASA is used concomitantly with naproxen, diclofenac or celecoxib; however, ibuprofen may interfere with ASA. To avoid any potential negation of its

antiplatelet effects, ASA should be administered a minimum of 30 minutes prior to or 8 hours after ibuprofen.^{3,12,13}

3. CV safety of NSAIDs: network meta-analysis

This meta-analysis pooled all randomized controlled trials that compared NSAIDs head-to-head or with placebo using a network methodology.⁸ The primary outcome was MI (fatal or nonfatal). Secondary outcomes were 1) stroke (hemorrhagic or ischemic fatal or nonfatal), 2) CV death, 3) death from any cause and 4) composite outcome of nonfatal MI, nonfatal stroke or CV death. A prespecified rate ratio (RR) of 1.3 was used as the primary threshold for increased CV risk. A total of 31 trials involving approximately 116,000 patients with any medical condition except cancer were included, and patients were allocated to naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib or placebo. (Etoricoxib is not marketed in Canada and rofecoxib and lumiracoxib were withdrawn from the Canadian market a few years ago.) Considering the outcome of MI, all drugs with the exception of naproxen, diclofenac and etoricoxib were associated with an increased risk compared with placebo. However, risk reached statistical significance only for rofecoxib (RR, 2.12; 95% CI, 1.26–3.56). All drugs were associated with an increased risk of stroke compared with placebo; risk reached statistical significance for ibuprofen (RR, 3.36; 95% CI, 1.00–11.60), diclofenac (RR, 2.86; 95% CI, 1.09–8.36) and lumiracoxib (RR, 2.81; 95% CI, 1.05–7.48). All drugs except naproxen showed some evidence of an increased risk of CV death, especially etoricoxib (RR, 4.07; 95% CI, 1.23–15.70) and diclofenac (RR, 3.98; 95% CI, 1.48–12.70). An increased risk of death from any cause was documented for all NSAIDs, but only diclofenac (RR, 2.31; 95% CI, 1.00–4.95) and rofecoxib (RR, 1.56; 95% CI, 1.04–2.23) were statistically significant. The authors concluded that naproxen appeared the least harmful in terms of CV safety, and they expressed confidence that ibuprofen, diclofenac, etoricoxib, rofecoxib and

lumiracoxib are associated with a risk increase of greater than 30% for several CV outcomes.

Discussion

Based on the available data, including the above-mentioned studies, naproxen appears to have a better CV safety profile than other NSAIDs and does not appear to significantly increase CV risks, specifically the risk of MI.^{6,8,9,14} Naproxen has a relatively long half-life of 14 hours and results in sustained inhibition of thromboxane production (an index of platelet COX-1 activity), whereas both ibuprofen and diclofenac have much shorter half-lives with more transient antiplatelet effects.² Celecoxib, the only COX-2 selective inhibitor currently available, is associated with lesser CV risk when used at lower doses and once-daily dosing (compared with higher dosages and twice-daily regimens).¹⁵ Patients often present with multiple risk factors (namely gastrointestinal and CV), and these are important considerations when deciding upon an NSAID.¹⁶

While a favourable trend for naproxen has been identified, limitations affect the strength of the study data. Meta-analyses are limited by the quality of the underlying data and the combination of reliable reporting of events and low event rates, as well as the limited access to unpublished safety data from the drug manufacturers. Due to the nature of the studies, it is difficult to make conclusions regarding various dosing regimens, as well as the intermittent use of NSAIDs commonly seen in practice.

Conclusion

While effective for their indication, NSAIDs—both nonselective and COX-2 selective—are not without risk. They should be used at the lowest effective dose for the shortest possible duration of therapy.² Health care professionals are responsible for considering each patient's individual risk factors when choosing the most appropriate therapy. If minimizing CV risk is an issue for a particular patient, naproxen should be considered. ■

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