EDITORIAL

Getting to the heart of the matter: a trialist's approach to the use of nonsteroidal anti-inflammatory drugs for patients with chronic pain syndromes

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In this editorial, I refer to the relative risks associated with different interventions. To provide a perspective of what it means, please consider the risks of particular events in the placebo group of controlled trials of cyclooxygenase-2 inhibitors: major vascular events (0.82%) including nonfatal myocardial infarction (MI; 0.29%) or any MI (0.33%), any stroke (0.36%), heart failure (0.26%), upper gastrointestinal (GI) bleeding (0.14%) with any major GI complication (0.19%).

Over the past 20 years, extensive research has evaluated the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which are traditional nonsteroidal drugs, and the newer cyclooxygenase-2 (COX-2) inhibitor drugs in the treatment of chronic pain syndromes. Perhaps no field has inspired more debate about which drugs to use at what doses and for what duration. The field has brought together researchers and clinicians from varied fields to discuss the risks and benefits of these therapies.

Before beginning a review of the evidence, it is important to note that there have been many positive developments as a result of this controversy. First, rheumatologists, chronic pain specialists, gastroenterologists, and cardiovascular specialists have come together to discuss the multidisciplinary management of our patients. This has made a tremendous advance in the field. Second, in earlier trials, nonselective NSAIDs were evaluated with less rigorous methodologies. This controversy has brought to light the safety of all NSAIDs and helped us weigh the evidence in a balanced fashion. Third, clinicians are now more likely to consult with other specialists before stopping medications, changing doses, or even prescribing new medications.

A full re-evaluation of the NSAID field began with the advent of the large clinical trials examining the safety and efficacy of COX-2 inhibitors. The VIGOR trial brought to light an important issue regarding cardiovascular risk. In the VIGOR trial, patients with rheumatoid arthritis treated with rofecoxib (50 mg daily) were more likely to develop myocardial infarction and overall cardiovascular (CV) events compared with those treated with naproxen (500 mg twice daily).[1] The Kaplan–Meier curves separated early and continued to separate over time. A meta-analysis of all rofecoxib trials indicated that there was a 2-fold increase in major CV events with the use of higher doses.[2] This opened the field to two important questions of whether: 1) COX-2-selective inhibitors were relatively unsafe when compared with a nonselective NSAID (i.e., naproxen); and 2) the dosing of a drug was an important causative factor in CV toxicity. In the ensuing years, many other trials emerged but 3 large-scale outcome trials, CLASS, TARGET, and MEDAL, evaluated the safety of a COX-2-selective inhibitor compared with a nonselective NSAID.[3-5] What became apparent was that the results of the trial could be gamed depending on which nonselective NSAID was

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the comparator. For example, in VIGOR, it was naproxen that was evaluated, whereas in TARGET it was both naproxen and ibuprofen. Finally, in MEDAL, diclofenac was studied. We then realized that there were a number of distinct features of NSAIDS beyond their COX-2 selectivity.

We identified 5 major predictors of CV toxicity.[6] They included: 1) the degree of COX-2 selectivity; 2) the effect of the NSAID on systolic blood pressure; 3) the half-life of the medication; 4) the dosing of the medication; and 5) the interaction of the NSAID with aspirin in patients at highest CV risk. What became apparent was that all NSAIDs, except for naproxen, were associated with some degree of increased ischemic CV risk and that across the board all agents were associated with an increased risk of heart failure. The number of predictors of cardiotoxicity informed us about the relative risk that was ultimately demonstrated in the large outcome trials. For example, rofecoxib is much more COX-2 selective than celecoxib and is associated with greater CV toxicity. Diclofenac and ibuprofen increase systolic blood pressure in patients with osteoarthritis and demonstrated greater cardiotoxicity when compared with celecoxib. The COX-2-selective lumiracoxib, evaluated in the TARGET trial, had less effect on blood pressure and a lower half-life leading to a better safety profile than ibuprofen. Finally, ibuprofen is known to negatively interact with aspirin when given together.

It is important to emphasize the benefits of COX-2 inhibitors. COX-2-selective drugs are associated with significant reductions in major gastrointestinal (GI) endpoints including upper and lower GI bleeding, ulceration, and perforation when compared with nonselective NSAIDs. In recent years, as the issue of CV toxicity loomed, there was a greater likelihood to use proton-pump inhibitors for gastroprotection in patients with chronic pain syndromes on NSAIDs, including COX-2-selective agents.

A recent meta-analysis, by Baigent et al.,[7] of over 350,000 subjects using NSAID for at least 4 weeks brought together key investigators to determine the best approach for our patients from both a GI and CV perspective to focus on the risk–benefit equation. There were two important observations from the meta-analysis that have reaffirmed our prior projections. Naproxen is not associated with an excess risk of major CV events and there is a doubling of the risk of heart failure causing hospital admission for all NSAIDs. As expected, selective COX-2 inhibitors lowered the risk of upper GI bleeding when compared with all nonselective NSAIDs. Importantly, naproxen had twice the GI hazard of all other nonselective NSAIDs. In terms of CV risk, the doses studied for COX-2--selective drugs and the non-naproxen nonselective NSAIDs, there was a 33% increase in major CV events. There was an increase of 75% in coronary events with no apparent excess risk of stroke. There was a 25% increase in total mortality. Based on this patient-level meta-analysis, we can conclude that high-dose naproxen avoids atherothrombotic risk but increases the risk of GI hazard, and that all other NSAIDs have comparable degrees of cardiotoxicity.

Putting this all together, when using a NSAID, be it COX-2-selective or a nonselective NSAIDs, one must consider giving these drugs intermittently at the lowest effective dose and at the lowest frequency. This is the overriding theme. Health care providers need to ask about over-the-counter nonselective NSAID use as part of history taking in patients with chronic pain. The best approach is the proposal constructed by Scheiman and Fendrick from the University of Michigan. It is a 2 × 2 table with low vs. high GI risk on the x-axis and low vs. high CV risk on the y-axis, producing 4 distinct boxes or patient categories.[8] For patients at low GI risk and low CV risk, any NSAID could be used. For patients at low GI risk and high CV risk, it is clear that naproxen is frontline therapy. Naproxen could be accompanied by a proton-pump inhibitor to provide maximal gastric protection. For patients at high GI risk and low CV risk, clearly celecoxib can be used safely and it is the drug of choice. Finally, for patients at high GI risk and high CV risk, nonpharmacological therapies in combination with moderate doses of acetaminophen (under 2 g per day) may be the strategy to use.[9] Since the use of opioids is also associated with increased CV risk, these agents are not an alternative except in very rare cases.[10] Finally, ibuprofen should be avoided in patients on aspirin as evidence is mounting that they negatively interact with each other.

The road has been long and the controversy has lingered. While we have learned that COX-2-selective inhibitors are not free of complications, more importantly, we have learned that nonselective NSAIDs are not without risks. For patients with severe chronic pain syndromes, withholding therapy is unacceptable and commonly used NSAIDs will be considered for pain control. NSAIDs should be used judiciously, weighing the risks and benefits, and, whenever possible, we should consider alternative pharmacologic and nonpharmacologic pain management strategies.

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