Coxibs and NSAIDs — clearing the air

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The introduction of cyclooxygenase-2 (COX-2) selective inhibitors (coxibs) for the treatment of osteoarthritis (OA), rheumatoid arthritis, and pain was heralded as a significant advance in the clinical armamentarium. Efficacy equal to those of the non-selective non-steroidal anti-inflammatory drugs (NSAIDs) associated with a safer toxicity profile, particularly as it related to gastrointestinal (GI) adverse events such as peptic ulcer, bleeding, obstruction, and perforation, led to a high level of enthusiasm with respect to their routine use. The estimated 16,500 deaths per year associated with GI bleeds in patients receiving non-selective NSAIDs, made the switch to coxibs especially attractive. Coxibs advantages were recognized in guidelines published by the American College of Rheumatology, EULAR (European League Against Rheumatism), and the American Pain Society recommending their use in arthritis and pain management.

An increased rate of cardiovascular (CV) events including acute myocardial infarction (AMI), stroke, and peripheral vascular thrombotic syndromes was first noted in the VIGOR study associated with the use of rofecoxib 50 mg daily. A large study of celecoxib at a dose of 400 mg b.i.d. which exhibited no increase in thromboembolic CV adverse events whether or not patients were using aspirin was reassuring regarding the question of a negative coxib-related CV class effect. However, the finding of increased CV events associated with rofecoxib 25 mg daily, in a colorectal adenoma chemoprevention trial (APPROVe) relative risk (RR) 1.92 for thrombotic events vs the placebo group, apparent only after 18 months of treatment, led to a voluntary withdrawal of rofecoxib from the world market, and a concern regarding possible potential for all coxibs to show a similar CV adverse event profile.

The issue as to whether this represented a class effect for COX-2 selective inhibitors was reintroduced when an increased CV risk was observed with celecoxib in a clinical trial for colorectal adenoma prevention (APC Trial), a composite CV end-point of death 2.8–3.1 years of follow-up from CV causes, including AMI, stroke, or heart failure was reached in 1% of the placebo group, 2.3% of the celecoxib 200 mg b.i.d. group, and 3.4% of subjects in the celecoxib 400 mg b.i.d. group. On the basis of these findings, the Data and Safety Monitoring Board recommended early discontinuation of the study. In contrast to this latter study, however, a similar clinical trial being carried out for adenoma prevention (PreSAP Trial) revealed no increase in fatal or non-fatal CV events in patients receiving celecoxib 400 mg/day as compared to placebo. An earlier unpublished study assessing the efficacy of celecoxib, 200 mg b.i.d., in limiting the progression of Alzheimer's disease was associated with an increase in CV events as compared to placebo; interpretation of the findings was complicated by imbalances in baseline medical history for subjects with regard to hypertension (HTN), diabetes and coronary artery disease; small sample size; small number of events decreasing robustness of results; and imbalance in randomization. A 1-year study of lumiracoxib, a new coxib under investigation, revealed a numerical, but not statistically significant, increase in CV events as compared to naproxen (hazard ratio = 1.77 [0.82–3.84], P = 0.15). Results of the 3-year ADAPT Trial, set up to compare the efficacy of celecoxib and naproxen in Alzheimer’s prevention, added a confusing and unexpected finding to the mix of observations. Subjects taking celecoxib, 200 mg twice daily, showed no increase in CV or cerebrovascular events; in contrast, there was a suggestive increase of CV events associated with sodium naproxen at 220 mg b.i.d., the over-the-counter (OTC) dose as compared to those taking placebo. In regard to the latter, in controlled trials, rofecoxib, lumiracoxib and etoricoxib exhibited a RR for CV events of 1.7–2.38 when compared to full-dose naproxen as a comparator.

In a similar vein, a CV risk was identified in patients receiving parecoxib (the precursor molecule to valdecoxib) and valdecoxib in two trials utilizing these agents for perioperative pain control in patients undergoing coronary-artery-bypass grafting surgery (CABG), no increase in CV events was noted, however, in similar trials in patients undergoing various non-CV surgical procedures. It is also noteworthy that all patients in the CABG trials also received co-treatment with low-dose aspirin. Therefore,
Prior observational studies showed no increase in risk of AMI related to celecoxib use. An as yet unpublished epidemiologic study on CV risks with coxibs and NSAIDs evaluated CV risk factors and NSAID use in a sample size of over 7 million persons per year enrolled in California Medicaid. This study had the advantage of available OTC aspirin data; no censoring at age 65; long durations of follow-up with low drop-out rates; and sicker populations than private-payers. The risk of AMI with celecoxib revealed no apparent increased risk of AMI at doses of 200 mg/day or less; valdecoxib also revealed no increased risk. Of interest was an increased risk of AMI with indomethacin, meloxicam, and sulindac. It was concluded that, as a class, non-coxib NSAIDs may increase CV risk; differences existed between non-coxib NSAIDs with respect to such risk; and that naproxen was not cardio-protective.

One mechanism whereby coxibs might be associated with increased CV risk is based on an imbalance between inhibition of thromboxane and prostacyclin. Coxibs would shift the trend toward thrombosis by inhibiting prostacyclin, a thrombosis-inhibiting prostaglandin while, at the same time, thrombosis-promoting thromboxane was not inhibited. A second mechanism which might pertain is an increase in HTN and edema, seen to various degrees both with non-selective NSAIDs and coxibs. This latter mechanism may explain observed increases in CV risk seen with non-selective NSAIDs.

The potential CV thrombotic effects attributed to the coxibs may be shared by other NSAIDs on a mechanistic basis, underscoring the complexity of the issue. Effective inhibition of platelet aggregation requires sustained > 80% inhibition of platelet COX-1, a level achieved by aspirin and high dose naproxen. Other NSAIDs, including low doses of ibuprofen (e.g., Advil), diclofenac, and meloxicam, amongst others do not achieve this degree of thromboxane inhibition throughout their dosing interval and may therefore, like coxibs, also result in unbalanced thromboxane-prostacyclin inhibition. This is important to consider when assessing the potential increased risk of OTC doses of NSAIDs (e.g., Aleve as compared to full-dose naproxen). Of related interest is the observation that acetaminophen, 500 mg, administered to healthy volunteers caused a marked reduction of prostacyclin synthesis for 6–8 h without any obvious effect on thromboxane synthesis, a pattern similar to that described with coxibs.

The non-selective NSAIDs have not been subjected to placebo-controlled long-term studies and where evaluated, non-naproxen NSAIDs did not differ from coxibs in long-term outcome studies where they served as comparators. Examples include diclofenac and ibuprofen in the Celecoxib Long-term Arthritis Safety Study (CLASS), ibuprofen in Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), and diclofenac in Etoricoxib Diclofenac Gastrointestinal Evaluation (EDGE) (Table I). Therefore, if the coxibs imparted CV risk in these 1-year studies, they would have performed no worse than ibuprofen and diclofenac. Indeed, in aspirin-treated patients studied in TARGET, the risk of CV events in patients receiving ibuprofen exceeded that of those who received lumiracoxib. The TARGET study once again raises the question whether short-acting NSAIDs, such as ibuprofen, interfere with the anti-platelet effect of low-dose aspirin. Even more perplexing is the observation that aspirin intake in a study of colorectal adenoma protection was associated with a dose-related numerical increase in frequency of AMI and stroke.

As noted, an important question is the issue as to whether the finding of increased CV events observed with rofecoxib represents a class effect or whether there are differences in coxibs in their CV risk profile. Differences between the CV risks associated with coxibs at usual dose schedules may be the result of the different half-lives and lower protein-binding; longer half-life and decreased protein-binding would allow more free drug to be active for a longer period following administration in a given patient.

Limitations in interpreting the above studies, some of which are contradictory in terms of their findings, may represent deficiencies inherent to short-term studies; differences in dosage schedules; and differences in patient populations who, at baseline, are at varying risks for myocardial events.

Subsequent to a United States Federal Drug Administration (FDA) review in April 2005, valdecoxib was, at the request of the FDA, voluntarily withdrawn from the market due to CV and cutaneous toxicity safety concerns. All marketed prescription NSAIDs, both non-COX-2 selective and COX-2 selective, were to require a revision in labeling to include a boxed warning, highlighting the potential for increased CV events and GI bleeding. In addition, the FDA requested manufacturers of non-prescription (over-the-counter) NSAIDs to include more specific information on potential CV and GI risks. In an FDA Executive Summary Report, it was deemed reasonable to conclude that there is a “class effect” for increased CV risk for all NSAIDs pending the availability of data from long-term controlled clinical trials more clearly delineating true relationships. Data at this point did not allow concluding that COX-2 selective drugs conferred an increased risk over non-selective NSAIDs in chronic use. This interpretation of available data would serve to alert physicians and patients that simply switching from a COX-2 selective agent to a non-selective COXibs does not mean that the potential for increased risk of serious adverse CV events has been fully, or even partially, mitigated.

The main issue is “where do we go from here”? NSAIDs have an increased risk of GI bleeding, perforation, and obstruction, especially in high risk patients with a history of past or present ulcer disease. Use of proton-pump inhibitors may protect the upper GI tract and also is effective on dyspepsia, but would not be protective for patients with respect to lower GI bleeds. Coxibs, on the other hand, are

<table>
<thead>
<tr>
<th>Trial</th>
<th>Diagnosis</th>
<th>Subjects (number)</th>
<th>COX-2</th>
<th>NSAIDs comparator</th>
<th>CV adverse events: coxibs vs NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS*</td>
<td>OA</td>
<td>5968</td>
<td>Celecoxib 400 mg twice daily for up to 15 months</td>
<td>Diclofenac 75 mg b.i.d.</td>
<td>No CV increase</td>
</tr>
<tr>
<td>TARGET*</td>
<td>OA</td>
<td>8773</td>
<td>Lumiracoxib 400 mg daily for 1 year</td>
<td>Ibuprofen 800 mg t.i.d.</td>
<td>No CV increase</td>
</tr>
<tr>
<td>EDGE*</td>
<td>OA</td>
<td>7111</td>
<td>Etoricoxib 90 mg daily for up to 16 months</td>
<td>Diclofenac 75 mg b.i.d.</td>
<td>No CV increase</td>
</tr>
</tbody>
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*Background <325 mg daily permitted.
associated with a decrease in GI risk, both upper and lower bowel. In patients receiving aspirin prophylaxis for AMI and stroke prevention, the use of ibuprofen has been shown to interfere with aspirin-binding to platelets, which could negate the aspirin-protective effect on CV risk. Such interference has been shown to occur with rofecoxib, valdecoxib, and diclofenac. Although diclofenac does not interfere with aspirin prophylaxis, this agent has been suggestively associated with increased CV risk. Naproxen, considered to have low CV risk when used in full doses, as noted earlier, has also been shown to interfere with the effect of aspirin on platelet COX-1 activity and function. Further complicating the issue is the observation that sudden cessation of long-term therapy with non-selective NSAIDs is associated with an increased risk of CV events within 30 days post-discontinuation of these agents, particularly in patients with rheumatoid arthritis or systemic lupus erythematosus. This may be the result of a rebound effect from platelet inhibition, as well as a decreased effect of the NSAIDs on CV inflammatory processes.

Individualizing therapy for each patient, carefully weighing risks and benefits, is essential. The uncertainty of CV risk potential for non-selective as well as COX-2 selective NSAIDs adds further complexity to therapeutic decision-making. Important in such therapeutic considerations is the recommendation by the FDA that, with a class effect of NSAIDs on CV risks as a baseline, other factors must be considered in determining the overall risk vs benefit profile for individual drugs within a class. Factors to be considered include demonstrated benefit of a given drug over other drugs in the class related to effectiveness, as well as differences in toxicity, making it important to maintain a range of options and NSAID class from which physicians and patients may choose.

As with any medication, use of the lowest dose for the shortest period of time that brings significant relief is always a good tenet. Intermittent use of both coxibs and non-selective NSAIDs is likely to be associated with decreased toxicity. Appropriate prospective randomized clinical trials to further define evidence for or against CV risk with both coxibs and non-selective NSAIDs are in order. Such studies are, unfortunately, difficult to design ethically since one would be most interested in carrying out these investigations in high CV risk patients. It is essential that we continue to review very complicated data in scientific fashion and with appropriate prospective randomized clinical trials to very complicated data in scientific fashion and with appropriate prospective randomized clinical trials to.

References