Length of Exposure to Vioxx for Toxicity

An article in the May edition of the Canadian Journal of Medicine (Lavesque 2006) points to an early increased risk of myocardial infarct (MI) in patients newly using Vioxx who are older than 65 years. The authors of this important study retrospectively analyzed charts from first hospital admission with a discharge diagnosis of acute MI, nonfatal or fatal. This elegantly constructed case controlled study consisted of 113,927 patients in the Quebec Healthcare database, mean age of 75.2 years, followed for an average of 2.4 years. In the year preceding the index date, 70.7% of case and control subjects received at least one NSAID prescription; 18.9% were current users and 51.8% past users. Consequently, 29.3% were classified as non-users (reference category) during this period. Prescriptions had a mean duration of 28 days. Among those who were currently exposed, 239 rofecoxib and 287 celecoxib users had an acute MI. There were 65 (27.2%) first-time users of rofecoxib, 41 (63.1%) of whom had not received other NSAIDs, including celecoxib, during follow-up (naive users). Among prevalent users of rofecoxib, 73 (42.0%) had used only rofecoxib (monotherapy) and 101 (58.0%) had received at least one other NSAID (switchers), the majority being to celecoxib.

There are at least four major learning points that are clarified from this research. First, Lavesque et al found that the relative risk (1.67) of MI was highest following first-time use of Vioxx. This is significant for emphasizing the immediate toxicity of Vioxx, and downplaying any necessity for re-exposure.

Second, myocardial ischemia occurred within a median of only 9 (6-13) days after initiation of therapy. A number of other studies have indicated various longer lengths of exposure necessary for Vioxx to cause increased cardiovascular morbidity and mortality.

Vioxx Gastrointestinal Outcomes Research (VIGOR, Bombardier 2000) 9 months

Adenomatous Polyp Prevention on Vioxx (APPROVe, Bresalier 2005) 18 months

It is however my impression that the data used to support licensure showed a trend toward divergence of Vioxx from placebo for adverse cardiovascular events at a much earlier time that officially acknowledged, even if not statistically significant.

Third, the risk of myocardial ischemia remained elevated for the first 7 days after rofecoxib was discontinued, returning to baseline between day 8 and 30. This is consistent with my own review of a large number of cases involving potential Vioxx-induced cardiovascular injury. A major variable in establishing a causal link after discontinuation of Vioxx depends on the status of the person's coronary arteries (per coronary angiogram or autopsy findings), their ability to induce and then metabolize

coagulation factors, concurrent use of aspirin and NSAIDs, and the presence of other risk factors (use of hormones, activity level, smoking status, family history, hypertension, diabetes, etc). Additionally, consideration must be given to the long half life (17 hours) of Voixx, and the half lives of any Vioxx-induced factors potentially involved in the pathologic process.

One should remember that the studies evaluating Vioxx for licensure were designed to demonstrate efficacy (primary endpoint), whereas safety data is only collected as a secondary endpoint. In addition, critical at-risk (MI, stroke) subpopulations were not included, and these excluded, not studied, people are exactly the types of individuals who are prescribed Vioxx:

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Angina, CHF, MI, CABG within 1 year,

Stroke or TIA within 2 years

Uncontrolled HTN.

Had these at-risk populations been enrolled, the relative risk of myocardial adverse effects would have certainly been much higher.

Lastly, the increased risk of ischemic damage to the heart did not increase with the length of treatment, nor did it decrease. These findings are consistent with a mechanism of risk inducement by Vioxx that depends on the induction and suppression or interference of a number of intracellular mediators (interleukins, coagulation factors).

The results of Lavesque et al (2006) are interesting, but should not at all be surprising, for a number of reasons:

The pharmacokinetics of Vioxx support good bioavailability, prolonged half-life, and fairly quick onset of action.

The mechanisms of action of Vioxx resulting in cardiotoxicity are well-understood and completely explain the potential for thrombo-embolic events involving the coronary and cerebrovascular systems.

The expected timeline for a toxic effect is completely consistent with the above two principles.

The increases in cardiovascular events due to Vioxx are found in the population at most risk: elderly, presence of multiple risk factors (sedentary, diabetic, hypertensive, elevated cholesterol).

Despite its appealing theoretical advantage, COX-2 selectivity (not the same as specificity) does not yield an increased safety profile relative to NSAIDs, except for gastrointestinal.

The concept that Vioxx is COX-2 specific, and thus contributes to its safety, may not necessarily be factual (Wallace et al, 1998).

Vioxx was never shown to have greater efficacy than non coxibs (naproxen, ibuprofen).

In concert with the above points, when evaluating cases for Vioxx-related injury, one should begin by establishing a complete list of risk factors that are present, clarify and document the exact periods of use, and define the supposed adverse event (locate the coronary angiogram, autopsy results, etc). Whenever a patient experiences an adverse outcome from a drug, and that adverse outcome is in concert with known pathophysiologic mechanisms consistent with that drug class, the question of individual causation is appropriate to raise.

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