The Vioxx withdrawal: Latest in the COX-2 controversies

The recent voluntary withdrawal of rofecoxib (Vioxx) from the market might seem to close one of the more contentious introductions of a new drug. Yet, with much money at stake and two other selective cyclooxygenase-2 (COX-2) inhibitors on the market, the controversies remain, and in many ways are more heated than ever.

On page 849 in this issue, Simon and Strand (two experienced rheumatologist pharmaceutical consultants and trialists who played an active role in the development of COX-2 inhibitors) comment on the withdrawal of rofecoxib from the market, and offer concrete suggestions as to how to manage patients who have been taking it.

In a future issue, Dr. Eric Topol will offer his perspective. Dr. Topol is chairman of cardiovascular medicine at The Cleveland Clinic, an extremely experienced trialist in cardiology, and critical of Merck (the maker of rofecoxib) and the US Food and Drug Administration (FDA) on this issue (see his editorial in the October 21, 2004 issue of *N Engl J Med*, page 1707).

Debate about these drugs has been polarized every step of the way, from the preclinical research through interpretation and application of the clinical trial data, marketing of competing products, widespread use, and postmarketing concerns regarding efficacy and cardiovascular safety.

What is the role of COX-2 isozymes? Although understanding the physiology of the COX isozymes may eventually help us prevent some cancers, early application focused on pain relief and protection of the upper gastrointestinal (GI) tract.

This early focus resulted from epidemiologic studies that showed that the use of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) was the most common identifiable cause of upper GI bleeding. Marketing of COX-2 drugs focused on the negative role of COX-2-generated prostaglandins in pain and inflammation and the positive role of COX-1-generated prostaglandins, which presumably protect the gastric mucosa. Unfortunately, the biologic roles of COX-1 and COX-2 were often oversimplified.

Which patients need a selective COX-2 inhibitor? Although the nonselective NSAIDs can cause life-threatening gastric toxicity, the risk for any single patient is fairly low—as suggested by the inconclusive results of some trials, such as the Celexocib Long-term Arthritis Safety Study (CLASS), which compared a COX-2 inhibitor with two nonselective NSAIDs. For many NSAID users, the extra cost of a selective COX-2 inhibitor may not be warranted. Additionally, critics of the wide use of COX-2 inhibitors argue that since many older patients using NSAIDs long-term should also be taking cardioprotective doses of aspirin (which also has some gastric toxicity), it makes more sense to use a combination of low-dose aspirin, a nonselective NSAID, and a proton pump inhibitor as a gastroprotective agent.

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Unfortunately, the heated debate on this topic has prompted clinicians to focus on which NSAID to prescribe instead of on the more important question of whether *any* NSAID is the best choice. For instance, some rheumatoid arthrits patients need more aggressive treatment with disease-modifying drugs, while some osteoarthritis patients might respond better to the use of analgesics, physical therapy, and mechanical aids.

Are selective COX-2 inhibitors prothrombotic? There has been a theoretical concern that COX-2 inhibitors have prothrombotic potential because of their effects on platelets and endothelial cells. But the early clinical trials were not designed to look for this and did not include enough patients who suffered myocardial infarction, stroke, or deep venous thrombosis to permit adequate assessment.

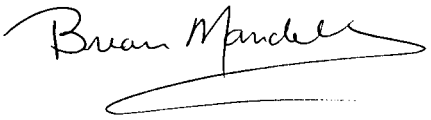
When more cardiovascular events occurred in the rofecoxib-treated group than in the naproxen group in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, a huge debate ensued as to whether rofecoxib was the culprit because of prothrombotic effects, or whether rofecoxib did not have a prothrombotic effect but rather the naproxen control group had fewer events because naproxen was cardioprotective.

Unfortunately, controlled clinical trial data usually do not explain the mechanism for an observation, and as a result, manufacturers of different COX-2 inhibitors fought over whether rofecoxib, as compared with other COX-2 inhibitors, was a dangerous drug. The sponsors of these drugs spent enormous energy and funds defending and attacking rofecoxib, analyzing additional trial data for cardiovascular risk, and recruiting physician support to their perspective. But the ideally powered trial of sufficient duration to address this concern has yet to be undertaken.

Topol and others argue that increased cardiovascular risk is a class effect of all COX-2 inhibitors, and the entire class of drugs is especially dangerous since they are so heavily prescribed. There are no strong data to support this contention, but there is a plausible mechanism to account for a prothrombotic state.

Defenders of the COX-2 inhibitors argue that absent any major warning signals, this approach is alarmist and requires more direct data before mandating any action. And they note that the chance of an adverse event happening to any single patient is quite small, especially if patients at higher risk for myocardial infarction are taking low-dose aspirin.

More FDA oversight or quick drug approval? The current debate highlights an FDA dilemma regarding drug approval. The agency has been under increasing pressure to streamline the drug approval process, in part to keep the cost of prescription drugs down, and to get new drugs to market sooner. But in the wake of the rofecoxib withdrawal there are calls for large, expensive, sustained trials of these and other drugs, which would slow the drug approval process and make it more expensive.



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SUGGESTED READING

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