By Charles Argoff, MD

Much Ado About COX-2

The FDA is reconsidering the safety risks of these popular analesgics. Should you do the same? Here's an update on where things stand.

It is safe to say that events over the past three months may significantly alter the way in which the FDA approves new medications, especially pain medications, as well as monitors these agents once they are released. The events I am referring to, of course, revolve around those regarding the use of COX-2 selective anti-inflammatory agents. Since Merck initiated a worldwide withdrawal in September 2004 of its COX-2 selective agent rofecoxib, following the observation in a clinical trial (APPROVe—Adenomatous Poly-Prevention on Vioxx) that use of the drug almost doubled the risk of cardiovascular and stroke if taken for 18 months or longer, many questions have been raised about the safety of this class of medication as a whole.

A Closer Look

The development of the COX-2 specific medications stemmed primarily from the observations that:

- There are at least two cyclooxygenase (COX) isoenzymes.
- The COX-1 isoenzyme is found primarily in blood vessel, stomach and kidney.
- The COX-2 isoenzyme is induced in the setting of inflammation by cytokines and other inflammatory mediators.
- COX-2 specific drugs would block this inflammatory response without significant effects on COX-1 function leading to antipyretic, analgesic and anti-inflammatory responses without the side effects of gastrointestinal bleeding and renal toxicity.

Recent events have indicated that it just isn't quite as simple as all that. In addition to safety issues, many have raised concerns regarding the over-marketing of this class of medication and the expense and other consequences that this may have led to.

Let's examine the safety concerns more closely. The APPROVe trial enrolled 2600 patients and compared rofecoxib 25mg/day to placebo. After 18 months, 25 patients taking placebo and 45 patients taking rofecoxib had experienced a confirmed thromboembolic event. In a previous study involving rofecoxib, known as the VIGOR (Vioxx Gastrointestinal Outcomes Research) study, Eric Topol of the Cleveland Clinic demonstrated that patients taking rofecoxib had a higher relative risk of developing adverse cardiovascular events than did patients using naproxen. Shortly thereafter, concerns rose regarding the use of valdecoxib and celecoxib; many have since called for their withdrawal from the market. Valdecoxib use in patients following heart surgery has been associated with an increased risk of cardiovascular events. Conflicting data have emerged about celecoxib, which will be summarized below.

In a study sponsored by the US National Cancer Institute examining the potential role of celecoxib in the prevention of colon cancer, patients in this five-year trial who received 400mg/day had a 2.5 fold increased risk of a major cardiovascular event and those patients who had received 800mg/day had a 3.4 fold increased risk of a major cardiovascular event compared to patients taking placebo.

Viewing this slightly differently, 2.2 percent of patients using celecoxib 400mg/day and three percent of patients using celecoxib 800mg/day had a cardiovascular event, compared with 0.9 percent of patients using a placebo. This trial involved 2400 patients with an average exposure to the drug of 33 months. In a separate pharmaceutical company-based study of patients with cancer, known as the PreSAP study, similar increased risks were not seen. In a third study involving this in which 2000 patients who are at high risk of developing Alzheimer's disease have been enrolled, a data monitoring board convened on December 10, 2004 and no changes in the study were recommended.

In a study which will be published in the February 2005 issue of *Annals of Internal Medicine*, Kimmel and associates have examined whether patients exposed to two different COX-2 specific agents, rofecoxib or celecoxib, have differing risks of experiencing a first nonfatal myocardial infarction. In this case-control study, 1718 patients with a first nonfatal myocardial infarction, from 36 hospitals in a five-county area, were compared to 6800 controls. The results indicated that the use of rofecoxib was associated with a statistically significant higher odds (2.72 greater) of myocardial infarction compared with the

use of celecoxib. The study also noted that patients using either drug were not at a significantly increased risk of having a myocardial infarction than those who did not use either drug, and that the celecoxib users appeared to have a *lower* risk of myocardial infarction than those who did not use either drug.

These initial data suggest that not all COX-2 drugs are created equally, but further study is required. Both government as well as commercial sources funded this study. Other experts remain concerned that the COX-2 specific drugs might still increase overall cardiovascular risk through a number of mechanisms, including inhibition of prostacyclin production.

Also quite recently, a study examining whether celecoxib or naproxen might reduce the risk of Alzheimer's disease was stopped after an increase in myocardial infarctions and strokes was noted in patients who were taking naproxen. Similar findings were not observed for those treated in this study with celecoxib. "Wait," you may say to yourself at this point, "I thought we were concerned about COX-2 specific drugs, but naproxen is a non-selective agent and there were no issues with celecoxib, the more specific drug in this study." Even the FDA is acknowledging that these data are a bit confusing!

Obviously, many issues remain regarding the interpretation of these data: different study designs, different quality of data, different study populations and the significance of the increased risks themselves. For example, many medications which we use commonly have equal or greater incidence of significant adverse effects yet we use these cautiously and judiciously with careful monitoring.

Other major concerns include the extent to which this class of medication was marketed as safer than the non-selective anti-inflammatory agents, when data which might have been available to only a few regarding the true risks associated with the use of this class of medication had been obtained. Of course, the reality is that, as a class, these medications are not generally more effective than non-selective medications so why are we so bent on using them?

These study results do provide preliminary data and the FDA will convene a panel next month to examine this class of medication more closely. Physicians should strongly consider the following interim recommendations by the FDA regarding the use of COX-2 selective agents:

1. Use the emerging information in considering the potential benefits and risks of these drugs.

2. The individual patient risk of a cardiovascular event and other anti-inflammatory agent side effects should be considered on a case-by-case basis.

3. Consumers have been advised that all over-the-counter drugs should be used strictly in accordance with the label.

Clearly, this story is far from being over. Stay tuned. **PN**