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# Painful lessons

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The serious side effects of pain relievers have been in the news lately. The increased risk of heart attacks and strokes associated with rofecoxib (Vioxx, Merck) and celecoxib (Celebrex, Pfizer) has led to the withdrawal of rofecoxib in late 2004 (the largest withdrawal in history) and reduced the sales of celecoxib by ~50%. In fact, the risk may be associated with the entire class of COX-2 selective inhibitors, and an advisory committee of the US Food and Drug Administration (FDA) will meet in mid-February 2005 to discuss the cardiovascular safety profile of these drugs. Because rofecoxib and celecoxib are top-selling prescription medicines, the issue has drawn widespread response. At a US congressional hearing, we heard testimony that the FDA failed to protect the public from unsafe drugs. In newspapers, we read about accusations that pharmaceutical companies knew of the increased cardiovascular risk associated with these drugs but delayed action. Calls for reforming the FDA abound, and, not surprisingly, lawyers across the country are drumming up clients for litigation against Merck and Pfizer. Added to all of this, the FDA recently issued a warning about cardiovascular risks associated with naproxen (Aleve, Bayer), and a study claimed that ibuprofen can cause damage to the small intestine. Although the naproxen warning has been questioned—by even the fiercest critics of COX2 inhibitors—as being a premature overreaction to the Vioxx debacle, it seems that no drug is safe when it comes to pain relief.

While the social and economic implications following the fall of COX-2 selective inhibitors continue to unfold, much less is being discussed about what this may mean to the scientific and drug discovery communities. After all, the development of rofecoxib and celecoxib represented the success of modern structure-based drug design. It also validated the general belief—at least until recently—that a detailed understanding of the players in biological processes, especially those involved in disease pathogenesis, would lead to better medicine.

COX-2 selective inhibitors belong to the family of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs reduce pain, fever and inflammation, but many can also lead to gastric bleeding, a side effect that can be life-threatening if left untreated (the cause of an estimated 16,000 deaths a year in the United States alone). It is thus a goal to develop a pain reliever without that potentially serious problem.

Both molecular and structural studies contributed to the development of such a drug. The first breakthrough was the identification of the molecular target of NSAIDs. One of the earliest NSAIDs was aspirin, a compound related to a substance in aspen tree bark. Although aspirin has been widely used for a long time, its molecular target—an enzyme called cyclooxygenase (COX)—was only identified in the 1970s. Cyclooxygenase catalyzes the first step of the synthesis of prostaglandins, a group of compounds involved in a variety of signaling processes, such as the inflammation response and the activation of platelet clumping.

In the 1980s, it was discovered that COX activity was induced at or near the site of inflammation. Further characterization showed that the activity is from the expression of a form of the enzyme (now called COX-2) distinct from the constitutively expressed enzyme (now called COX-1). The correlation of COX-2 expression with inflammation led to the hypothesis that selective inhibition of COX-2 may be a way to reduce inflammation without the undesirable gastric bleeding side effect.

Another important step forward in the development came from the crystal structures of both COX-1 and COX-2 in complex with inhibitors in the mid-1990s. These structures revealed that the active sites of the two enzymes are very similar. This observation is not surprising because they catalyze the same reaction. Nevertheless, there is one crucial difference: COX-2 has a side pocket extending from the active site, and this difference was exploited for the design of selective inhibitors.

Indeed, the designed inhibitors preferentially inhibit COX-2 over COX-1 at the molecular level; they are as effective as nonselective NSAIDs; and they cause less damage to the stomach when viewed by endoscopy. All of these indications suggested that the drugs would be good for those who suffer from chronic inflammation and pain, such as arthritis patients. In the late 1990s, rofecoxib and celecoxib were approved to treat osteoarthritis and rheumatoid arthritis. The success also prompted pharmaceutical companies to further pursue the next generation of inhibitors with even higher specificity toward COX-2.

Similar to the development of imatinib (Gleevec, Novartis), the success of rofecoxib and celecoxib validated the concept that drugs targeted to specific molecules have fewer side effects, at least until recently. The problem facing rofecoxib and celecoxib—that they avoided gastric bleeding only to incur the severe side effects of heart attacks and strokes—seems to contradict this particular strategy. However, one only needs to look closely at the initial assumption about COX-2 inhibition to realize that perhaps inhibiting COX-2 would not be specific enough. It is now known that the roles of COX-1 and COX-2 may overlap. In addition, COX-2 has been found to be constitutively expressed in several other tissues in addition to being induced at sites of inflammation. This suggests that the activity of the enzyme is involved in other processes and is consistent with the observation that some of the COX-2 selective inhibitors seem to affect the levels of prostaglandins involved in dilating blood vessels or activating platelet clumping.

The fall of COX-2 selective inhibitors may be discouraging news, but it highlights the importance of a full understanding of the target in question. Basic research is now necessary to understand the complex roles of COX enzymes in various biological processes and to identify new anti-inflammation targets other than COX-2. Perhaps specific inhibitors downstream of the prostaglandin pathway would alleviate the unacceptable cardiovascular risks. Nevertheless, the case is a clear reminder that all drugs have side effects; the question is whether their benefits outweigh their risks. ■