Coxibs: can this class of drugs survive?

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The sudden voluntary withdrawal of rofecoxib (Vioxx), a "selective" cyclooxygenase 2 (Cox-2) inhibitor, by Merck & Co on September 30, 2004, as a result of its adverse cardiovascular effects (Couzin 2004), begs the question as to whether this toxicity is a class effect. There is little doubt that toxicity associated with a drug can permeate and have a devastating effect on the clinical use of the entire class to which the drug belongs, unless the nature of that toxicity is clearly defined and characterized in a transparent fashion within the scientific community. In this particular case, the jury is still out. However, unless this class of drugs is used appropriately and wisely, it will not survive.

Clinically, selective Cox-2 inhibitors and nonsteroidal antiinflammatory drugs (NSAIDs) are used in the treatment of arthritis, a degenerative disease of the joints. The symptoms of arthritis can include pain, heat, redness, swelling, stiffness, and/or restriction of movement. The most common forms of arthritis are rheumatoid and osteoarthritis. The former is a chronic inflammatory disease of joints characterized by marked inflammation of the synovial membrane and articular structures along with muscle atrophy, whereas the pathology of the latter relates to loss of articular cartilage, bone remodeling with possible hypertrophy of the bone at margins, and changes in synovial membrane. Arthritis is believed to be a major cause of morbidity and disability in the population at large. The discovery of Cox-2 inhibitors was considered an outright breakthrough in the management of pain and inflammation in arthritic patients without concomitant problems of gastrointestinal disturbances and ulceration, but nothing is that simple.

The beneficial effects of this class of drugs are believed to be due to selective inhibition of the Cox enzyme. The enzymes Cox-1 and Cox-2 are involved in the catabolism of eicosanoids from arachidonic acid. Among these ecosanoids are prostacyclin I_2 (PGI_2) and thromboxane A_2 (TxA_2). Both play a critical role in blood vessel function. Where PGI_2 is a substance that produces vasodilatation and inhibits platelet aggregation, TxA_2 is a potent vasoconstrictor that promotes platelet aggregation (Catella-Lawson 2001). In the past, Cox-1 was thought to be the constitutive enzyme present in tissues such as platelets, vascular endothelial cells, and gastric epithelial cells, whereas Cox-2 was the inducible form; ie, its expression would be induced by pathophysiological conditions, eg, inflammation. However, evidence has accumulated to suggest that Cox-2 is an enzyme primarily responsible for the synthesis of PGI_2, whereas Cox-1 is believed to be responsible for the synthesis of TxA_2 in platelets (Vinals et al 1997; Brock et al 1999; Catella-Lawson et al 1999; McAdam et al 1999). It has also been suggested that Cox-2 has cardioprotective properties (FitzGerald 2002). Thus, given that the selective inhibition of Cox-2 may have been expected to result in some detrimental effects on the cardiovascular system, it would have been prudent to use these compounds cautiously in patients with existing cardiovascular pathology.

However, no issue in clinical pharmacology is so straightforward, and post-hoc analysis of data for coxibs, rofecoxib, and celecoxib has provided contradictory conclusions regarding cardiovascular safety. Evidence to suggest that the use of coxibs could produce significant detrimental cardiovascular effects was first brought to light in the peer-reviewed medical literature by Murkherjee and colleagues (2001). The authors analyzed data from randomized clinical trials (VIGOR, CLASS trials, Study 085, and Study 090) for protective or hazardous effect associated with the use of Cox-2 inhibitors. They concluded that both rofecoxib (0.74%; $p = 0.04$) and celecoxib (0.8%; $p = 0.02$) treatment produced a higher risk of unwanted vascular events (eg, myocardial infarction) when compared with placebo (0.52%) (Murkherjee et al 2001). In contrast to the latter, a subsequent report by Konstam and colleagues (2001) using a combined analysis of individual patient data and assessing cardiovascular thrombotic events (hemorrhagic, unknown deaths, nonfatal myocardial infarction, and nonfatal strokes) in patients treated with rofecoxib suggests there was no evidence of excess cardiovascular events for rofecoxib compared with either placebo (0.84; 95% CI: 0.51–1.38) or the non-naproxen NSAIDs (0.79; 95% CI: 0.40–1.55) that were studied. The authors of the latter study suggested that one reason for the Murkherjee et al (2001) investigation to conclude that Cox-2 inhibition would result in greater cardiovascular thrombotic events was that absolute event rates across different trials were employed for meta-analysis and, in their

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view, this is considerably less reliable (Konstam et al 2001). As well, post-hoc analysis of data from CLASS and SUCCESS trials by White and colleagues (2003) suggests there is also no greater risk of cardiovascular thrombotic events (1.06; 95% CI: 0.70–1.61; p = 0.79) associated with celecoxib versus conventional NSAIDs or placebo (White et al 2003).

A recent article published prior to the withdrawal of rofecoxib, which reviewed the evidence for the risk of thromboembolic events associated with Cox-2 inhibitors, came to the conclusion that selective Cox-2 inhibitors should be prescribed with caution and only in patients where such therapy is warranted (Clark et al 2004). Many interesting issues were addressed in this review in comparing and contrasting the perceived basis for the adverse effects of rofecoxib and celecoxib. One issue that was touched upon was the concept of selectivity for Cox-2 versus Cox-1, and one reason as to why celecoxib may have less adverse cardiovascular effects was its lower selectivity for Cox-2 when compared with rofecoxib (Table 1), which is a reasonable assumption. Should this be the case, then more selective compounds may show a greater incidence of adverse cardiovascular effects in patients at risk. It is also interesting that the dose of rofecoxib employed in the latest trial that resulted in its withdrawal from the market was a lower one (25mg daily) (Singh 2004) than in the VIGOR trial (50mg daily) (Bombardier et al 2000). The lower dose would have been expected to produce less inhibition of Cox-1, and this may have manifested in greater adverse cardiovascular effects in patients prone to vascular problems.

More recently, a meta-analysis of pooled data from two studies involving valdecoxib in patients who underwent coronary artery bypass graft procedures suggests an increased risk of myocardial infarction and stroke by more than twofold. The relative risk being 2.19 (CI 1.19–4.03; p = 0.01) (Liano 2004, online). It should be noted that the latter analysis has not been peer-reviewed; however, complete data from one of the trials reviewed were published in a full paper last year. It indicates that the total number of myocardial infarction, stroke, and death is fourfold higher in the patients treated with Cox-2 inhibitors compared with the placebo group (Ott et al 2003). Interestingly, analysis of adverse effects individually; ie, deaths, cerebrovascular disorders, and myocardial infarction in patients treated with Cox-2 inhibitors compared with placebo indicates no significance difference between the drug treatment versus placebo group. Valdecoxib has a 30-fold selectivity for Cox-2 versus Cox-1 (Table 1).

Table 1 The ratio of IC_{50} for Cox-2, Cox-1, and plasma half-life of four Coxibs

Drug names	IC_{50} Cox-2 / Cox-1	$t_{1/2}$ (hour)
Rofecoxib	35[a]	9.9–17.5[b]
Celecoxib	7.6[a]	5.1–10.5[c]
Valdecoxib	30[a]	7–8[d]
Etoricoxib	106[a]	24.8[e]

[a] Clark et al (2004); [b] Depre et al (2000); [c] Werner et al (2002); [d] Fenton et al (2004); [e] Rodrigues et al (2003).

Admittedly, for a curious pharmacologist, the critical question of whether the adverse cardiovascular effect of coxibs is a class effect still must remain a mystery. Without the clear cut evidence to suggest that the adverse effect is a class effect in a population without vascular risk, selective Cox-2 inhibitors still remain a viable option in the treatment of rheumatoid arthritis and osteoarthritis in patients who may have serious gastrointestinal problems with regards to bleeding. A critical question is whether more selective compounds that may offer better protection in the gastrointestinal tract are more likely to produce a greater incidence of cardiovascular and thrombotic events. Moreover, will molecules that have a lower selectivity for Cox-2 versus Cox-1 offer any gastrointestinal protection on a long-term basis? Needless to say the use of these drugs will require very careful monitoring in patients and selective use may have to be implemented if we are to avoid losing the entire class. It would appear that three simple reasons may prevent this class of drugs from gaining wide acceptance in mainstream clinical practice in the future and eventually be responsible for the demise of the entire class. They include: (1) convoluted and not very transparent analysis of clinical data from trials; (2) lack of rigorous peer-review of data and information from clinical trials; and (3) inappropriate clinical use in a population of patients at risk of vascular mortality.

Finally, it is perhaps rudimentary to suggest that the survival of coxibs in clinical practice may very much depend on pharmacokinetic and pharmacodynamic characteristics of the molecule in question (Table 1). Simply put, the combination of greater selectivity for the Cox-2 isozyme and a prolonged half-life may not be the most favorable profile that an agent needs to possess if it is to be used widely and successfully against rheumatoid arthritis and osteoarthritis in patients with vascular disorders. The combination of high selectivity for Cox-2 and a prolonged plasma half-life can result in the accumulation of the drug in the body leading to enhanced inhibition of PGI_2 formation, and rampant elevation of TxA_2 levels during the course of

therapy. Both are in turn expected to increase the likelihood of adverse cardiovascular events such as stroke and myocardial infarction.

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