Cyclo-oxygenase (COX) or prostaglandin endoperoxidase H synthase inhibitors are important contributors to the treatment of arthritis and other inflammatory conditions. Cyclo-oxygenases catalyze the conversion of arachidonic acid and \( \text{O}_2 \) to PGH\(_2\), the committed step in prostaglandin synthesis (1). The two isoenzymes, COX-1 and COX-2, are encoded by separate genes located on different chromosomes. The COX-2 expression can be induced through multiple signaling pathways involving protein kinases A and C, tyrosine kinases and bacterial endotoxin, among others (1). Both isoenzymes are homodimeric, heme-containing glycosylated proteins with two catalytic sites (1). They are targets of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs); aspirin, a nonselective COX-1 (cyclo-oxygenase) and COX-2 inhibitor may result in gastric toxicity. For this reason, selective COX-2 inhibitors have been developed to reduce erosion of the gastric mucosa. Both selective and nonselective NSAIDs reduce prostacyclin formation in the infarcted heart; they accomplish this by tipping the balance of prostacyclin/thromboxane in favor of thromboxane, a prothrombotic eicosanoid. The relative increase in thromboxane, coupled with a diminution in prostacyclin in infarcted heart muscle, can lead to the development of thrombotic cardiovascular events. This may be prevented by the addition of a nitric oxide donor to NSAIDs. (J Am Coll Cardiol 2002;39:521–2) © 2002 by the American College of Cardiology.

**Why Do Cyclo-Oxygenase-2 Inhibitors Cause Cardiovascular Events?**

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This report confirms evidence that selective nonsteroidal anti-inflammatory drugs (NSAIDs), such as celecoxib, can lead to thrombotic cardiovascular events. Aspirin, a nonselective COX-1 and COX-2 inhibitor may result in gastric toxicity. For this reason, selective COX-2 inhibitors have been developed to reduce erosion of the gastric mucosa. Both selective and nonselective NSAIDs reduce prostacyclin formation in the infarcted heart; they accomplish this by tipping the balance of prostacyclin/thromboxane in favor of thromboxane, a prothrombotic eicosanoid. The relative increase in thromboxane, coupled with a diminution in prostacyclin in infarcted heart muscle, can lead to the development of thrombotic cardiovascular events. This may be prevented by the addition of a nitric oxide donor to NSAIDs. (J Am Coll Cardiol 2002;39:521–2) © 2002 by the American College of Cardiology.

Cyclo-oxygenase (COX) or prostaglandin endoperoxidase H synthase inhibitors are important contributors to the treatment of arthritis and other inflammatory conditions. Cyclo-oxygenases catalyze the conversion of arachidonic acid and \( \text{O}_2 \) to PGH\(_2\), the committed step in prostaglandin synthesis (1). The two isoenzymes, COX-1 and COX-2, are encoded by separate genes located on different chromosomes. The COX-2 expression can be induced through multiple signaling pathways involving protein kinases A and C, tyrosine kinases and bacterial endotoxin, among others (1). Both isoenzymes are homodimeric, heme-containing glycosylated proteins with two catalytic sites (1). They are targets of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs); aspirin, a nonselective NSAID, acts via COX-1 to inhibit platelet thromboxane A\(_2\) formation and, therefore, lowers mortality from ischemic heart disease (1). Inhibition of COX-2 reduces inflammation, fever and probably colon cancer (2,3). Covalent modifications of COX enzymes by aspirin cause permanent inactivation of the enzyme (1). Because of their anti-inflammatory action, COX inhibitors have been selected for long-term treatment of inflammatory conditions. The COX-2 inhibitors predispose to erosion of the gastric mucosa with subsequent hemorrhage. Both COX-2 selective and nonselective COX inhibitors cause renal toxicity with papillary necrosis and interstitial nephritis (4).

Recently, Mukherjee et al. (5) analyzed clinical trials dealing with the effect of celecoxib and rofecoxib, two selective COX-2 inhibitors, on cardiovascular events. They concluded that these two inhibitors are responsible for a significant risk of cardiovascular thrombotic events. Based on one of the clinical trials (Vioxx Gastrointestinal Outcomes Research), they showed that the relative risk of developing thrombotic cardiovascular events such as myocardial infarction or unstable angina was high as compared to naproxen, a nonselective COX inhibitor (5). The investigators conclude that COX-2 inhibition favors prothrombotic events by tipping the balance of prostacyclin/thromboxane in favor of thromboxane, a prethrombotic eicosanoid (5). Experimental data have confirmed these conclusions.

The release of prostaglandins from ischemic tissue was first demonstrated by McGiff et al. (6). The heart metabolizes arachidonic acid into different prostaglandins (7), particularly prostacyclin (8). An increase in prostaglandins in canine coronary venous blood occurs during postocclusive reactive hyperemia (9). Acute myocardial ischemia not only increases prostacyclin but also thromboxane in coronary vein blood (10). Prostacyclin increases in microsomes prepared from infarcted myocardium (10). It is likely that macrophages are the main source of prostaglandins and thromboxane (11). Production of prostacyclin and thromboxane by the infarcted heart in situ occurs in conjunction with increased activation of the inducible form of nitric oxide synthase (iNOS) (12). The induction of iNOS in the ischemic rabbit and human heart increases the coronary arterial-venous coronary difference of \( \text{NO}_2\) and \( \text{NO}_3\) (\( \text{NO}_x\)). Activation of iNOS occurs primarily by activated macrophages during the inflammatory phase (12).

Both nitric oxide (NO) and prostaglandins play an important role in the infarcted heart (2). Prostacyclin is a vasodilator that prevents cardiac arrhythmias and platelet aggregation; thromboxane, in contrast, promotes platelet aggregation, acts as a vasoconstrictor and initiates ventricular arrhythmias (2). Nitric oxide counteracts thromboxane, inhibits platelet aggregation and compensates for the NSAIDs’ induced reduction of prostacyclin (2).
of thromboxane and prostacyclin in the infarcted rabbit heart has been confirmed together with increased upgrading of iNOS (9). The interaction between COX and iNOS is due to an iron-heme center as the active site of COX (9). Exogenous NO, together with cytokine-induced NO, enhances both COX isoenzymes (9). Upgrading of COX-2 protein by cytokines is also accomplished by NSAIDs. This action differs from upgrading by inflammatory cytokines, which increase COX at the transcriptional levels (13).

Recently, we obtained evidence of changes in the prostacyclin/thromboxane ratio after celecoxib, which lowers myocardial prostacyclin production in infarcted heart muscle, but fails to inhibit thromboxane (14). Therefore, celecoxib (5 mg/kg) tips the balance of prostacyclin/thromboxane in favor of thromboxane, leading to increased vascular and thrombotic events (14). In contrast, the non-selective COX inhibitor aspirin (35 mg/kg/d) suppresses both prostacyclin and thromboxane (15).

Both NO and prostacyclin counteract the effect of thromboxane on platelet aggregation and, therefore, on thrombotic events (2,16). Nitric oxide is particularly important in the presence of diminished prostacyclin or unchanged and increased thromboxane. Celecoxib does not inhibit induction of iNOS, but decreases the ratio of prostacyclin/thromboxane (14). Prostacyclin and NO have an additional and different impact on the infarcted heart and tumor progression. For example, prostacyclin increases the potential for stimulating growth of new blood vessels in cancer and the infarcted heart muscle. Angiogenesis in tumors is undesirable because it may promote the spread of the tumor; it plays an important positive role in healing and remodeling of the infarcted heart (3).

How can one avoid these thrombotic events following NSAIDs? One possibility is to supplement COX-2 inhibitors with small doses of aspirin, as suggested by Mukherjee et al. (5). Another possibility is the combination of the COX-2 inhibitors with a NO donor, B-NOD; this is a newly developed NO donor that can be administered orally, its effect persisting for more than 7 h, causing no drop in blood pressure nor an increase in heart rate; it increases cyclic guanosine monophosphate and prevents platelet aggregation. In vitro, release of NO by B-NOD is augmented by the presence of blood platelets (17). We had previously suggested that a combination of aspirin with a NO donor may prevent the decline of prostacyclin after aspirin alone and celecoxib (8,13). The relative proportion of each component would have to be determined. A combination of NSAIDs and B-NOD has already been used to prevent renal depletion of prostacyclin in situ following administration of aspirin (18).

It is realized that re-evaluation of a commercially successful compound is not a desirable course. Conversely, science should not be hampered by a matter of expediency. Progress depends on re-evaluation of known facts; there are no immovable objects in either science or medicine.

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