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EDITORIAL COMMENT

Cyclooxygenase Inhibition in Patients With Coronary Artery Disease*

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The prostanoids are receptor-activating lipid mediators that exert a pervasive influence on body functioning because they involve all organ systems and their effects can be heightened by various disease states and pathophysiologic conditions (1). The enzyme cyclooxygenase (COX) catalyzes the intracellular rate-limiting step in the formation of various prostanoids from arachidonic acid. These prostanoids include the prostaglandins PGD_2, PGE_2, PGF_2, $PGF_{2\alpha}$, and PGI_2 (prostacyclin) and the procoagulant thromboxane (TXA_2), found in blood platelets (2). The multiplicity of prostaglandin and TXA_2 receptors and their signaling systems has yielded a combined molecular biologic, biochemical, and pharmacologic-physiologic approach that has defined their structures, distribution, properties, and function (1).

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There are also two known isoforms of the COX enzyme, COX-1 and COX-2. Cyclooxygenase-1 is expressed in most body tissues and is the only COX isoform present in blood platelets. In platelets, it converts arachidonic acid into TXA_2 and is the main isoform found in the gastric mucosa, where it catalyzes the cytoprotective prostaglandins (1,2). Unlike COX-1, COX-2 appears to be less involved in normal physiologic activity but is expressed more prominently with active inflammation and other pathophysiologic processes (2,3). It was this latter observation that led to the clinical development of selective COX-2 inhibitors that would provide clinical anti-inflammatory activity while sparing the cytoprotective prostaglandins produced by the gastric mucosa (4).

In addition to the prostanoids produced by COX activity, there are analogs of prostaglandins known as isoprostanes that can be formed by oxygen-derived free radical attack on arachidonic acid as well as by COX (5,6). Some of these isoprostanes, such as 8-epi-$PGF_{2\alpha}$, have biologic activities similar to TXA_2 (7). In human atherosclerosis, there is a marked elevation in both TXA_2 and epi-$PGF_{2\alpha}$, which may be contributing to the increased risk of thrombosis and restenosis in patients undergoing coronary angioplasty. The formation of epi-$PGF_{2\alpha}$ with increased thromboxane activity may be induced by COX-2, which could bypass TXA_2 formed by COX-1. Therefore, a drug such as aspirin, which inhibits platelet TXA_2, might not be effective as an anticoagulant in all patients.

Aspirin has been shown to be beneficial in reducing the risk of myocardial infarction and stroke in patients with atherosclerosis (8). The critical action of aspirin on platelets is the inhibition of PGH_2 production by COX-1 because PGH_2 is the obligatory precursor of TXA_2, the final product of platelet metabolism of arachidonic acid via COX-1 and TXA_2 synthetase activity (8).

In patients with unstable angina, another factor, one that is not attributable to platelets, appears to be operative and responsible for TXA_2 production by both COX-1 and COX-2 that is associated with atherosclerotic plaques (9). In a significant number of patients, thromboxane production is only partially inhibited by aspirin, as reflected by the urinary excretion of thromboxane metabolites despite complete suppression of TXA_2 formation by aspirin in platelets (10). Atherosclerotic plaques and contiguous tissue of the diseased arteries are the presumed source of aspirin-insensitive TXA_2. Aspirin also inhibits prostacyclin formation from endothelial cells (8). Prostacyclin has vascular protective action (vasodilator, inhibitor of platelet aggregation, and mesenchymal proliferation); however, the concomitant suppression of TXA_2 predominates, and the functional consequence is cardioprotection (8).

Traditional nonsteroidal anti-inflammatory drugs also inhibit COX-1-derived TXA_2 and COX-derived prostacyclin. However, the effect is reversible during the dosing interval, and this transient effect would not be expected to provide cardioprotection (2). There are also recent data to suggest that the use of a nonsteroidal anti-inflammatory drug might inhibit the benefits of aspirin (11).

The selective COX-2 inhibitors can inhibit prostacyclin formation in atherosclerotic blood vessels, while having no effects on COX-1-derived TXA_2. The net effect would be a potentiation of thrombotic activity (3). However, COX-2 inhibition might also inhibit the formation of prothrombotic isoprostanes, such as 8-epi-$PGF_{2\alpha}$.

The study by Kearney et al. (12) in this issue of the *Journal* sought out to test the hypothesis that the addition of the COX-2 inhibitor nimesulide would provide an additional antiplatelet effect over that of concomitant aspirin use in patients undergoing coronary angioplasty. However, the results of the study showed no additional effect of adding nimesulide to aspirin on TXA_2 levels and no effect of the aspirin-nimesulide combination on the levels of the isoprostane 8-epi-$PGF_{2\alpha}$ (12). The addition of nimesulide to aspirin did cause a reduction in prostacyclin production (12).

This important study confirms past observations regarding the effects of aspirin and selective COX-2 inhibitors on TXA_2 and prostacyclin production while showing that the

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production of 8-epi-$PGF_{2\alpha}$ is not enzymatically derived through COX activity (1,8). Optimal suppression of TXA_2 is achieved by the use of aspirin alone; however, in patients with atherosclerosis, not all thromboxane-like activity is inhibited by aspirin (e.g., 8-epi-$PGF_{2\alpha}$) (12).

In addition to aspirin, pharmacologic approaches that have been used to achieve greater suppression of TXA_2 actions have included agents that directly block the TXA_2/PGH_2 receptor, agents that interfere with thromboxane synthetase, and agents that provide combined thromboxane synthesis inhibition and TXA_2/PGH_2 receptor blockade (8). These agents would also preserve prostacyclin synthesis; however, the clinical studies to date show no benefit beyond what is observed with aspirin (8). A potential strategy would be a pharmacologic intervention that would interfere with the production and/or activity of 8-epi-$PGF_{2\alpha}$ to be used with aspirin for maximizing antiplatelet activity.

As shown by Kearney et al. (12), selective COX-2 inhibitors do not effect TXA_2 production and may decrease the production of prostacyclin, suggesting potential harm from using these drugs in patients with atherosclerotic vascular disease. However, most of the available data suggest no clinical risk, and the results of a recent study suggest that COX-2 inhibitors may, in fact, be protective in patients with coronary artery disease because of their potent anti-inflammatory actions, which manifest as improved endothelium-dependent vasodilation with reductions in C-reactive protein levels and oxidized low-density lipoprotein plasma levels (13).

However, because of current concerns regarding the cardiovascular safety of selective COX-2 inhibitors, current guidelines suggest that arthritic patients with cardiovascular disease risk factors should receive low-dose aspirin when being prescribed a selective COX-2 inhibitor (1). Once TXA_2-mediated platelet aggregation is sufficiently blocked by aspirin, the additional pleiotropic actions of COX-2 inhibitors related to their anti-inflammatory actions may come into play and could provide an overall beneficial effect on cardiovascular outcomes. Much evidence is now accumulating that unstable coronary artery disease may be an active inflammatory process (14,15). Clinical trials need to be conducted to test this intriguing new hypothesis that anti-inflammatory drug treatment with COX-2 inhibition can actually protect against unstable cardiovascular syndromes.

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