CHAPTER 7

COX-2 INHIBITORS AND CARDIOVASCULAR RISK

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Abstract: The development of drugs that selectively inhibit cyclooxygenase-2 (COX-2) demonstrates translational research from bench to bedside based on underlying knowledge of micro-cellular structure and function. However, theoretical concerns about potentially pro-thrombotic effects of selective COX-2 inhibitors coupled with observations of increased cardiovascular risk have produced significant consternation and lead to the withdrawal of two of these agents from the market. A number of questions remain unanswered. It appears clear that both selective and non-selective COX inhibitors are associated with increases in blood pressure. In addition, blood pressure is often increased after starting nonsteroidal therapy, and we know that even small increases in blood pressure in subjects with pre-existing vascular disease are associated with substantial increases in the risk of cardiovascular morbidity. Given this line of reasoning, one might hypothesize that the observed increases in the risk of cardiovascular events associated with COX-inhibitors are largely due to increases in blood pressure in populations of subjects who are already at high risk. But can we generalize that the adverse cardiovascular effects observed for

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rofecoxib and valdecoxib are sufficient to indict the entire class of COX-2 inhibitors, or is this not a class effect, but dependent upon the degree of COX-2 selectivity? In either case, it seems prudent to recommend that subjects who are at higher risk for a cardiovascular event and receiving a COX-inhibitor should also be treated with low dose ASA with close follow up of blood pressure and efficacious use of anti-hypertensive medications. Finally, modest dietary salt restriction may help lessen the effects of COX-inhibitors on blood pressure.

1. REVIEW OF PROSTANOID PRODUCTION

Prostaglandins (PGs) are critical mediators of a number of physiological processes including the regulation of vascular homeostasis and thrombosis, as well as inflammation. Arachidonic acid, which is liberated from membrane-bound phospholipids by phospholipase A2, is catalyzed by the enzyme cyclooxygenase (COX). Because COX has two catalytic moieties, a cyclooxygenase and a peroxidase, this enzymatic complex is also referred to as the prostaglandin G/H synthase (PGHS).

Cyclooxygenase initially generates the unstable endoperoxide intermediate, prostaglandin G2 (PGG2), which it then catalyzes to prostaglandin H2 (PGH2). Following the production of PGH2, further enzymatic processes are needed to form the active prostanoids. Enzymes specific for each tissue (tissue-specific enzymes) catalyze PGH2 to biologically active prostanoids: prostaglandin I2 (PGI2, or prostacyclin) synthase produces prostacyclin, thromboxane A2 (TxA2) synthase produces thromboxane, and prostaglandin D2, E2, and F2 synthases produce their respective prostaglandins: PGD2, PGE2, and PGF2 (Figure 1). PGI2 and TxA2 are probably the most important prostanoids in the regulation of vascular homeostasis, since they have opposing effects on platelet function.

Because the rate-limiting step in the production of prostaglandins is the COX enzyme, COX inhibitors can have potent effects. Although it does not appear that either PGG2 or PGH2 have direct biological effects, inhibition of COX results in a decrease in the substrate availability for a given tissue’s prostanoid synthases.

There are at least two related but distinct gene products that possess cyclooxygenase activity, COX-1 and COX-2. These cyclooxygenase isoforms are differentially expressed and regulated throughout the vascular system. Initial evidence suggested that COX-1 was constitutively and ubiquitously expressed, and COX-1 was therefore regarded as a housekeeping enzyme. In contrast, COX-2 was thought to be strictly an inducible enzyme, up-regulated by diverse mitogenic and proinflammatory factors, such as bacterial lipopolysaccharides, cytokines such as interleukin-1, and phorbol esters. It is now known that this initial construct for the COX isoforms was too simplistic. It has been demonstrated that COX-2 is constitutively expressed in a variety of tissues, including vascular endothelial cells, renal medullary cells, and cells of the macula densa. In addition, there is evidence that COX-1 is inducible under certain conditions. Of note, a third enzyme termed COX-3 has been identified and appears to be a variant of COX-1. COX-3 may be a target for acetaminophen.