COX-2 INHIBITORS

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Introduction:

The primary effect of the NSAIDs is to inhibit cyclooxygenase (COX or prostaglandin synthase), thereby impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. Two related isoforms of the COX enzyme have been described, COX-1 and COX-2. The most important differences between the two isoforms are the regulation and expression of the enzymes in various tissues:

1. COX-1 is expressed in most tissues. It is described as a "housekeeping" enzyme, regulating normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function), and is stimulated by hormones or growth factors.

2. COX-2 is usually undetectable in most tissues; its expression is increased during states of inflammation. COX-2 is constitutively expressed in the brain, kidney, bone, and probably in the female reproductive system.

Thus, differences in the effectiveness with which a particular NSAID inhibits an isoform of cyclooxygenase may affect both its activity and toxicity. It has been proposed that the perfect NSAID would inhibit the inducible COX-2 isoform (thereby decreasing inflammation) without having any effect on the constitutive COX-1 isoform (thereby minimizing toxicity). Such an agent would maximize effectiveness, without inducing toxicity, particularly gastroduodenal erosions.

Specific COX-2 Inhibitors:

Selective COX-2 inhibitors, celecoxib (Celebrex), rofecoxib (Vioxx), and valdecoxib (Bextra) are approved for use in rheumatoid arthritis and osteoarthritis while rofecoxib and celecoxib are approved for use in acute pain. Valdecoxib has been approved for dysmenorrhea as well. These drugs have at least a 200 to 300-fold selectivity for inhibition of COX-2 over COX-1.

Benefits and Side Effects of COX-2 Inhibitors:

The principal benefit with the selective COX-2 inhibitors is the production of comparable analgesia and antiinflammatory effects to the nonselective NSAIDs, but with fewer symptomatic gastric and duodenal ulcers and a decrease in gastrointestinal symptoms. An additional benefit is possible protection against the development of colon cancer.

1. Many clinical trials have confirmed the efficacy and relative lack of gastroduodenal toxicity of all of the selective COX-2 inhibitors when compared to nonselective NSAIDs.

2. Generation of prostanoids by activated platelets plays an important role in platelet function and in promoting vasoconstriction. Since production of the potent prostanoid, thromboxane A2, is dependent upon COX-1, inhibition of COX-2 alone should produce little or no effect upon platelet function.

3. The lack of an inhibitory effect on platelet function of the selective COX-2 inhibitors, as noted above, may be valuable when an antiinflammatory effect is needed for a patient who is receiving on-going anticoagulation.

References:

1991; 324:1716.