CLINICAL PHARMACOLOGY OF CYCLOOXYGENASE INHIBITORS

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The prostaglandin (PG)H-synthase pathway of arachidonic acid metabolism generates ubiquitously bioactive prostanoids that participate in the local modulation of many important pathophysiologic functions, including gastrointestinal (GI) cytoprotection, primary hemostasis, cardiovascular homeostasis, arterial thromboresistance, inflammatory reactions, cell proliferation and apoptosis.[1] PGH-synthase is an integral membrane protein with two distinct catalytic activities, a cyclooxygenase (COX) activity that converts arachidonic acid into PGG_2 and a hydroperoxidase (HOX) activity that reduces PGG_2 to PGH_2. The latter is the substrate of at least 6 downstream isomerases, that are responsible for the tissue-specific synthesis of individual prostanoids. PGH-synthase exists in two isoforms, that are products of different genes, ie PGH-synthase 1 (also referred to as COX-1) and PGH-synthase 2 (also referred to as COX-2).[2] Aspirin is a relatively selective COX-1 inhibitor at low-doses (75-100 mg) given once daily, that completely and persistently suppress thromboxane (TX)A_2-dependent platelet aggregation, despite its 20-min half-life. This is due to the permanent nature of platelet COX-1 inactivation by aspirin, through selective acetylation of a single serine residue (Ser-529) within the COX-1 channel. Aspirin can also inhibit COX-2, but this requires higher doses (because of different conformation of the COX-2 channel) and more frequent dosing (because of the rapid *de novo* synthesis of the enzyme in nucleated cells). Low-dose aspirin is an effective antithrombotic drug reducing the risk of major vascular events (non-fatal myocardial infarction, non fatal stroke as vascular death) by approximately 25% in a variety of high-risk vascular disorders. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) have long been known to be associated with reduced risk of colo-rectal cancer in observational studies, but because of their substantial GI toxicity have never been tested in long-term randomized studies of chemoprevention, with the notable exception of relatively small studies of sulindac in patients with familial adenomatous polyposis (FAP). Most traditional NSAIDs are non-selective inhibitors of COX-1 and COX-2, but individual compounds (eg, diclofenac) display moderate COX-2 selectivity, both *in vitro* and *ex vivo*.[5] The coxibs represent a relatively new class of selective COX-2 inhibitors developed to reduce the burden of GI toxicity associated with traditional NSAIDs. Two independent studies, VIGOR and TARGET, with two structurally unrelated compounds, ie rofecoxib and lumiracoxib, respectively, have demonstrated that 1-year administration of these drugs is associated with 50 to 65% lower risk of upper GI complications than traditional NSAIDs. However, when tested in 3-year, placebo-controlled chemoprevention studies, two structurally unrelated compounds, ie rofecoxib and celecoxib, have been associated with a 2- to 3-fold increased risk of major vascular events. These findings have led to a voluntary withdrawal of rofecoxib but not of celecoxib. A recently completed meta-analysis of all the randomized coxib trials suggests that the size of the increased risk of vascular events is somewhat smaller (approx 40%) than suggested by individual studies; is largely confined to an increased risk of myocardial infarction, and is shared by some traditional NSAIDs, ie ibuprofen and diclofenac.

1) FitzGerald GA. COX-2 and beyond: Approaches to prostaglandin inhibition in human disease. Nat Rev Drug Discov 2003; 2:879-890 – 2) Fitzpatrick FA, Soberman R. Regulated formation of eicosanoids. J Clin Invest. 2001; 107:1347-1351.