Editorial

Cyclooxygenase-2 inhibitors and inflammatory bowel disease

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Cyclooxygenase (COX) enzyme-dependent arachidonic acid metabolites occupy key positions in important physiologic processes such as immunity, reproduction, and vascular integrity.[1] There are two known isoforms of COX, 1 and 2. COX-1 is a constitutive enzyme, important for mucosal integrity that produces cytoprotective and anti-inflammatory prostaglandins. COX-2 is the inducible form of the enzyme and is markedly increased at sites of inflammation. The two COX genes have been cloned, and expression of COX-2 mRNA and protein has been shown to be elevated in several human inflammatory processes including inflammatory bowel disease (IBD) and malignancies, as well as in animal models of IBD and carcinogenesis. In this regard, recent evidence has implicated COX-2 in gastric, esophageal and colorectal carcinogenesis. Indeed, increased COX-2 expression was noticed in Barrett's esophagus and esophageal adenocarcinomas, gastric carcinomas, and colorectal adenomas and carcinomas.[2] COX-2 appears to be mutagenic and tumorigenic in vitro. Moreover, COX-2 overexpression may inhibit apoptosis and increases invasiveness of malignant cells.[2] In addition, COX-2 overexpression enhances prostaglandin (PG) synthesis and the importance of prostaglandins (PGE_2) in the progression of a chronic inflammation or neoplasia has long been recognized. Although the release of these compounds in response to tissue injury seems to be a key event in the reparative process and inflammatory response, it is becoming clear that they are implicated in cell proliferation and inhibition of immune surveillance; therefore, overproduction of PGs could favor malignant growth.[2] Specifically, high levels of proinflammatory leukotrienes (LTs) and up-regulated expression of COX-2 are characteristic of inflammation, including IBD, and have been implicated in cell survival and early colon carcinogenesis.[3] LTs cause a time- and dose-dependent increase in expression and/or membrane accumulation of COX-2, beta-catenin, and Bcl-2, as well as PGE_2 production, and the effects of LTs on these transformation-associated proteins correlate well with the ability of LTs to reduce programmed cell death.[3] Therefore, these observations suggest that IBD is associated with the expression and distribution of proteins that are characteristic of transformed cells and such pathological conditions may involve a signaling mechanism comprising an altered rate of apoptosis.[3] On the other hand, inhibition of COX-2 prevents growth of cancer xenografts in nude mice, and aspirin use (which inhibits both COX-1 and COX-2) decreases the risk of developing malignancy.[2] Also, COX-2 inhibition results in suppression of neoplastic polyps in the APC knockout mouse, a model of familial adenomatous polyposis. Specifically, there are already strong indications that inhibitors of the NF-κB-regulated gene COX-2; e.g., celecoxib and aspirin prevent colon cancer. Indeed, celecoxib inhibits NF-κB activation through inhibition of IκBK and Akt activation leading to downregulation of synthesis of COX-2 and other genes needed for inflammation, proliferation and carcinogenesis.[4] Therefore, applying COX-2 selective (or nonselective) inhibitors reduces inflammation, suppresses carcinogenesis in the gastrointestinal (GI) tract and could be an effective and promising way to prevent cancer.[2]

Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit both COX isoforms are efficacious in the treatment of arthritis, although they also result in significant GI toxicity. Selective inhibitors of the COX-2 isoform (which is thought to mediate inflammation) such as celecoxib, etoricoxib, lumiracoxib, rofecoxib, and valdecoxib have been developed to preserve mucosal integrity by maintaining normal GI tissue concentrations of COX-1. GI toxicity could thereby be decreased while still

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providing effective relief of pain and inflammation. Controlled trials of the COX-2 inhibitors in patients with rheumatoid arthritis have demonstrated significantly decreased rates of gastroduodenal ulcer formation and GI complications when compared to traditional NSAIDs. However, although there are fewer complications, they still occur and can be serious.

Focus on IBD, the use of NSAIDs has been associated to the onset and relapse of Crohn's disease and ulcerative colitis, and these drugs are not indicated in IBD.[5] Specifically, NSAIDs were listed in the practice guidelines of the American College of Gastroenterology among factors recognized to exacerbate IBD.[6] This contraindication is a problem for those patients who suffer from IBD-associated inflammatory arthropathies. In view of IBD disease flare with NSAID use, it is reasonable to postulate that the GI toxicity with selective COX-2 inhibitors may be less in IBD patients, similar to findings in the general population and in patients with arthritis. However, recent evidence suggests that treatment with COX-2 inhibitors is also associated with a high incidence of exacerbation of the underlying IBD and GI-related complications.[7] While COX-2 inhibitors including rofecoxib and celecoxib are effective in treating minor arthralgias in almost two thirds of IBD patients. However, drug-related side effects with exacerbation of IBD, including abdominal pain and bloody stools, requiring drug discontinuation may be observed (in one-quarter of patients), although with a lower frequency than NSAIDs.[5,8] Some evidence suggests the possible use of COX-2 inhibitors in inactive IBD, but a careful follow up is required for the possible appearance of drug-related side effects requiring drug discontinuation.[5]

Clinical use of COX-2-selective compounds has ignited strong debates regarding potential side effects, most notably those within the cardiovascular system such as myocardial infarctions, strokes, and elevation in blood pressure.[9]

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