Selective cyclooxygenase-2 inhibitors in inflammatory bowel disease

Sir,

The gastric (ulcer-producing) adverse relationship of conventional non-steroidal antiinflammatory drugs (NSAIDs) is now well recognized. NSAIDs non-specifically inhibit the cyclooxygenase enzymes (COX-1 and COX-2) leading to loss of gastric mucosal integrity and at the same time producing the desired antiinflammatory effect. It has been proposed that selective COX-2 inhibitors (coxibs) are non-toxic to the gastrointestinal tract by sparing COX-1 while retaining the potential antiinflammatory effect. It was on this background that the NSAIDs, particularly the selective COX-2 inhibitors were indicated in inflammatory bowel disease (IBD). However, recent reports indicate conflicting clinical observations (exacerbation or amelioration) of IBD with the use of coxibs, the new COX-2 inhibitors.

Long-term administration of COX-2 inhibitors to knockout mice (genetically COX-2 deficient) led to development of significant intestinal pathology suggesting that COX-2 products are involved in the maintenance of bowel integrity. The mechanism(s) underlying the intestinal damage and aggravation by coxibs have been poorly explored. COX-2 expression was reported to be increased in the colonic mucosa in both experimental colitis and colitis of IBD, suggesting its protective role in healing. It could thus be speculated that the suppression of elevated COX-2 levels by coxibs leads to further deterioration of active IBD. First-degree relatives of patients with Crohn’s disease experienced increase in small bowel permeability with use of coxibs. A genetic component may also be involved in IBD.

However, it remains uncertain whether the coxibs-mediated increase is linked to the depletion of cytoprotective prostaglandins derived via this isoform or whether it is due to the mucosal exposure of luminal antigens that trigger local inflammatory reaction. Recently, a new role of COX-2 in the maintenance of oral tolerance has been suggested. The tolerance of the intestinal immune system is assumed to be disrupted in IBD, thus causing enhanced reactivity of mucosal flora.

Further, the induction of COX-2 enzyme in apical and lamina propria mononuclear cells of the intestine in IBD patients suggests a function for COX-2 in repairing damaged tissue. Moreover, coxibs do not provoke injury on previously normal intestine. Thus, it is theoretically possible that active IBD might be even more specifically worsened by coxibs.

Though the clinical evidence is still preliminary these observations raise concern regarding the use of coxibs in preex-}

isting IBD. However, the chemopreventive activity of coxibs against colorectal carcinomas arising from ulcerative colitis might further justify the potential application of selective COX-2 inhibitors in IBD.

Thus, at the moment, the use of coxibs in patients with inflammatory bowel disease should be viewed with the same caution as with the use of conventional NSAIDs.

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