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EDITORIAL

Exacerbation of inflammatory bowel disease by nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors: Fact or fiction?

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Abstract

The existence of a possible link between inflammatory bowel disease (IBD) and nonsteroidal anti-inflammatory drugs (NSAIDs) has been repeatedly suggested. Recently, a few studies have addressed the issue of a possible, similar effect by selective cyclooxygenase-2 inhibitors (COXIBs). The present article reviews the available scientific evidence for this controversial subject.

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Key words: COX-2 inhibitor; Inflammatory bowel disease; Non-steroidal anti-inflammatory drugs

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The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with the onset of inflammatory bowel disease (IBD) or with a clinical flare-up of IBD in a number of case reports[1]. Both rectal and colonic frank ulcerations[2], small bowel ulcers[3] and intestinal, diaphragm-like strictures[1,3,4] have been reported after prolonged NSAID intake. On the other hand, no relationship is reported between NSAID treatment and exacerbation of underlying IBD[5,6].

The absence of controlled, prospective trials makes it difficult to draw definitive conclusions. Uncontrolled clinical experience suggests that anti-inflammatory agents can occasionally elicit relapse of IBD[7] and therefore should be employed with caution in patients with either ulcerative colitis or Crohn's disease. A recent systematic review of the available medical literature concluded that the epidemiological evidence for a positive link between NSAID exposure and relapse of IBD is weak, while admitting that "some patients with IBD do relapse when given NSAIDs[8].

Given the inconsistency of the conflicting data concerning the relationship between NSAIDs and IBD, the possible effect of selective cyclooxygenase-2 inhibitors (COXIBs) in this respect remains even more controversial. In order to better understand the relationship between anti-inflammatory treatment and IBD it is necessary to consider the possible pathogenetic mechanisms involved in the adverse effects on the bowel by non-selective NSAIDs. Several mechanisms have been postulated, such as enhanced intestinal permeability[9], enterohepatic recirculation of NSAIDS and formation of drug enterocyte adducts , the latter phenomena having been observed in animal studies[9] but never demonstrated in humans.

The major mechanism involved, however, is thought to be the inhibition of colonic prostaglandin synthesis[10], in particular of the COX-2 isoform. In the inflamed colon COX-2 expression is upregulated in an effort to repair mucosal damage[11] and its inhibition may result in exacerbation of colonic injury and in impairment of the mucosal repair processes elicited by the COX-2 enzyme[12]. In this respect both NSAIDs and COX-2 inhibitors could hamper the progression of the inflammatory state toward healing. On the other hand, if COX-2 is important in the reparative mechanisms in IBD, then patients with quiescent disease should have a lower risk of flare-up when taking NSAIDs[13].

The studies on the effect of COX-2 inhibitors on animal models of colitis have yielded conflicting results[9,14] even taking in account the differences in experimental conditions, type and dosages of the employed compounds. The only available study on human colonic mucosa, carried out on colonic biopsies taken in IBD patients, found that a highly selective COX-2 inhibitor, L-745337 inhibits local release of PGE2 and PGI2 to the same extent as indomethacin, a nonselective NSAID[15], an effect which would likely promote aggravation of mucosal damage..

In a clinical setting a perspective, open-label study in IBD patients with associated arthropathy rofecoxib, administered at a dose of up to 25 mg daily for 20 d, failed to elicit any flare-up of the intestinal disease[16]. Similarly, a retrospective analysis of IBD patients treated with

either celecoxib or rofecoxib for periods ranging from one week to 22 mo[17]. apparently confirmed the safety of COX-2 inhibitors in this respect. By contrast, a clinical exacerbation of the underlying IBD that subsided after the drug was discontinued, has been reported in 19% of patients taking rofecoxib[18]. In keeping with this finding a recent retrospective study in IBD patients taking either celecoxib or rofecoxib has found clinical relapse of the intestinal disease in 39% of cases, again with resolution of symptoms after COX-2 inhibitor withdrawal[19].

On the other hand, the first multicenter, random, double-blind, placebo-controlled study performed in USA ,taking into consideration of both clinical and endoscopic parameters, has shown that celecoxib 200 mg bid for 2 wk is as safe as placebo in patients with ulcerative colitis in remission[20].

Thus, as with nonselective NSAIDs, the available data remain conflicting and confusing. Summing up, on theoretical ground both NSAIDs and COX-2 inhibitors appear capable of triggering a flare-up of IBD by inhibiting the intestinal production of prostaglandins involved in the tissue reparative processes. In clinical practice, although clear-cut evidence is difficult to obtain due to the variable incidence of IBD reactivation and the paucity of prospective, controlled studies, both types of anti-inflammatory agents may precipitate recurrence of intestinal symptoms and therefore should be avoided, when possible, in patients with ulcerative colitis or Crohn's disease.

REFERENCES

1 **Bjarnason I,** Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology* 1993; **104:** 1832-1847

2 **Kurahara K,** Matsumoto T, Iida M, Honda K, Yao T, Fujishima M. Clinical and endoscopic features of nonsteroidal anti-inflammatory drug-induced colonic ulcerations. *Am J Gastroenterol* 2001; **96:** 473-480

3 **Smale S,** Tibble J, Sigthorsson G, Bjarnason I. Epidemiology and differential diagnosis of NSAID-induced injury to the mucosa of the small intestine. *Best Pract Res Clin Gastroenterol* 2001; **15:** 723-738

4 **Bjarnason I,** Price AB, Zanelli G, Smethurst P, Burke M, Gumpel JM, Levi AJ. Clinicopathological features of nonsteroidal antiinflammatory drug-induced small intestinal strictures. *Gastroenterology* 1988; **94:** 1070-1074

5 **Bonner GF,** Walczak M, Kitchen L, Bayona M. Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol* 2000; **95:** 1946-1948

6 **Dominitz JA,** Boyko EJ. Association between analgesic use and inflammtory bowel disease flares. A retrospective cohort study. *Gastroenterology* 2000; **115:** A3024

7 **Felder JB,** Korelitz BI, Rajapakse R, Schwarz S, Horatagis AP, Gleim G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol* 2000; **95:** 1949-1954

8 **Forrest K,** Symmons D, Foster P. Systematic review: is ingestion of paracetamol or non-steroidal anti-inflammatory drugs associated with exacerbations of inflammatory bowel disease? *Aliment Pharmacol Ther* 2004; **20:** 1035-1043

9 **Cipolla G,** Crema F, Sacco S, Moro E, de Ponti F, Frigo G. Nonsteroidal anti-inflammatory drugs and inflammatory bowel disease: current perspectives. *Pharmacol Res* 2002; **46:** 1-6

10 **Wallace JL.** Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. *Gastroenterology* 1997; **112:** 1000-1016

11 **Riley SA,** Mani V, Goodman MJ, Lucas S. Why do patients with ulcerative colitis relapse? *Gut* 1990; **31:** 179-183

12 **O'Brien J.** Nonsteroidal anti-inflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol* 2000; **95:** 1859-1861

13 **Bonner GF.** Using COX-2 inhibitors in IBD: anti-inflammatories inflame a controversy. *Am J Gastroenterol* 2002; **97:** 783-785

14 **Singh VP,** Patil CS, Jain NK, Kulkarni SK. Aggravation of inflammatory bowel disease by cyclooxygenase-2 inhibitors in rats. *Pharmacology* 2004; **72:** 77-84

15 **McCartney SA,** Mitchell JA, Fairclough PD, Farthing MJ, Warner TD. Selective COX-2 inhibitors and human inflammatory bowel disease. *Aliment Pharmacol Ther* 1999; **13:** 1115-1117

16 **Reinisch W,** Miehsler W, Dejaco C, Harrer M, Waldhoer T, Lichtenberger C, Vogelsang H. An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia. *Aliment Pharmacol Ther* 2003; **17:** 1371-1380

17 **Mahadevan U,** Loftus EV Jr, Tremaine WJ, Sandborn WJ. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. *Am J Gastroenterol* 2002; **97:** 910-914

18 **Biancone L,** Tosti C, De Nigris F, Fantini M, Pallone F. Selective cyclooxygenase-2 inhibitors and relapse of inflammatory bowel disease. *Gastroenterology* 2003; **125:** 637-638

19 **Matuk R,** Crawford J, Abreu MT, Targan SR, Vasiliauskas EA, Papadakis KA. The spectrum of gastrointestinal toxicity and effect on disease activity of selective cyclooxygenase-2 inhibitors in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10:** 352-356

20 **Sandborn WJ,** Stenson WT, Brynskov J, Steidle G, Robbins J. Safety of celecoxib in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol* 2004; **99 (Suppl.10):** S257

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