Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality?

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REVIEW ARTICLE

Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality?

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Abstract
Background Nonsteroidal anti-inflammatory drugs (NSAIDs), conventional and selective cyclooxygenase-2 (COX-2) inhibitors, are among the most widely used medications for the treatment of various inflammatory conditions. There is strong evidence of a possible association between the use of these drugs and the relapse of inflammatory bowel diseases (IBD).
Objective Our objective was to examine the literature regarding the exacerbation of IBD associated with the use of conventional NSAIDs and selective COX-2 inhibitors and the underlying pathogenetic mechanisms.
Study design We reviewed articles, including original papers, controlled trials, case reports, reviews, and editorials published in English at the PubMed, Scopus Database, and Science Direct database, searching with the following keywords: nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, Coxibs, inflammatory bowel diseases (IBD), ulcerative colitis (UC), Crohn's disease (CD).
Results There is substantial evidence that exacerbation of IBD happens after treatment with NSAIDs, but the available data remain conflicting, and it is not clear whether selective COX-2 inhibitors are safer than traditional NSAIDs. However, there is some evidence that selective COX-2 inhibition and COX-1 inhibition (with low-dose aspirin) appear to be well-tolerated in the short term. Regarding the mechanisms of relapse, the reduction of prostaglandins appears to be the hallmark of the NSAIDs adverse effects.
Conclusions Further randomized, double-blind, controlled trials should be performed to address this issue, and more in vitro studies to identify the pathways involved are required.

Keywords NSAIDs · Inflammatory bowel diseases · COX-1 · COX-2 · COX-2 inhibitors · Coxibs

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Introduction

A possible association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the relapse of inflammatory bowel diseases (IBD) has been repeatedly suggested [1]. IBD include Crohn's disease (CD) and ulcerative colitis (UC) and are chronic heterogeneous disorders of the intestine resulting from multifactorial environmental precipitants in genetically susceptible individuals [2]. IBD patients seek relief in NSAIDs for non-IBD-related pains (arthralgias, arthritides) [3], and these drugs are also prescribed for the symptoms of extraintestinal manifestations of IBD, such as peripheral arthritis, sacroiliitis, ankylosing spondylitis, and osteoporosis-related fractures [4]. NSAIDs are considered to be the first-line treatment for the abnormalities just mentioned (i.e, relieve pain and treat inflammation), although immunosuppressive and biological agents [methotrexate (MTX), thalidomide, tumor necrosis factor alpha (TNF-α) antigen] have also been used [5]. They inhibit the production of both cyclooxygenase enzymes (COX-1 and COX-2), and thereby decrease the production of prostaglandins (PG) [6] that leads to the anti-inflammatory, antipyretic, and analgesic effects of NSAIDs

[7, 8]. They also have topical actions such as surface membrane phospholipid interaction and effect on mitochondrial energy (acidity, lipophilicity) [4].

NSAIDs, which are the most prevalent and severe cause of drug toxicity in the USA [9], cause initial onset of IBD, reactivate quiescent disease [10], and are responsible for gastrointestinal (GI) complications (i.e., gastropathy and enteropathy) [4]. There is a higher than expected use of NSAIDs among patients admitted to hospital for flares of IBD [10]. A probable contributing factor in leading to an exacerbation of colitis by NSAIDs is inhibition of colonic PG synthesis [11]. This leads to de novo colitis and aggravation of preexisting intestinal disease. Selective COX-2 inhibitors were produced in the hope that they lack these digestive toxicities, as they are specifically targeted to IBD; however, their use requires similar cautions to the use of NSAIDs [12, 13].

A large number of people suffering from IBD take NSAIDs and COX-2 inhibitors for various reasons, as the efficiency of these drugs in pain control seems to be unquestioned. In some patients, exacerbation disease exacerbation happens; however, it is uncertain whether NSAIDs are implicated in IBD relapse or whether COX-2 inhibitors are safer than NSAIDs. NSAIDs have been implicated in the onset or the exacerbation of IBD in a number of studies and case reports [13, 14], whereas in other studies, no relationship has been found between NSAID treatment and an increase in significant disease flares [15, 16]. On the other hand, COX-2 inhibitors have a smaller incidence of toxicity to the small bowel or colon [10], as recent studies indicate that COX-2 inhibitors are prescribed more often than NSAIDs in patients who are older, sicker, and have risk factors associated with NSAID gastropathy [17]. Is the concept that the use of NSAIDs is associated with relapse of IBD true or false? The answer to this question is still very complicated, and there are many different issues to be addressed regarding this subject, such as the following:

- Are NSAIDs in general implicated in exacerbation of IBD?
- Are COX-2 inhibitors safe in patients with IBD?
- Do COX-2 inhibitors induce clinical relapse in patients with IBD or/and de novo colitis?
- COX-2 inhibitors appear to control pain in most of IBD patients, but are they still responsible for exacerbation?
- Are COX-2 inhibitors connected to GI symptoms in patients with IBD?
- Do COX-2 inhibitors safety and efficacy profile warrant further evaluation in controlled trials?
- Are COX-2 inhibitors, COX-1 inhibitors and low dose aspirin well-tolerated in the short-term treatment?
- Do Corticosteroids in combination with COX-2 inhibitors lead to IBD exacerbation in a short period of time?

This review provides updated information on traditional NSAIDs, COX-1 and COX-2 inhibitors whether they cause exacerbation of IBD or not, indicating details regarding their safety, efficacy, and mechanisms of their actions.

NSAIDs in general and exacerbation of IBD

Various studies have shown that conventional NSAIDs trigger more frequent relapse of preexisting intestinal inflammation than inducing de novo colitis [18, 19]. In experimental models of animals, the damage was initiated by various combinations of the three biochemical actions common to all conventional NSAIDs [19, 20], such as COX-1 and COX-2 inhibition and local effect. The latter was thought to involve an NSAID surface-membrane phospholipid interaction [21] and an effect on mitochondrial energy metabolism. These effects were consequent to the physicochemical properties of conventional NSAIDs, namely, acidity and lipophilicity [4]. Clinical relapse of IBD after treatment with NSAIDs was associated with escalating intestinal inflammatory activity similar to the clinical course seen in patients with active IBD not taking NSAIDs [22, 23]. It was suggested that the relapse might be triggered by dual inhibition of the enzymes, and it was clear that the nonselective NSAIDs were associated with clinical relapse [23]. There is increasing evidence that the main pathophysiologic consequence of COX-1 inhibition is impaired mucosal microcirculatory blood flow [20], whereas the COX-2 enzyme might have an immunomodulatory role in the GI tract [24].

Takeuchi et al. [4], examining the possible association between relapse in IBD and use of NSAIDs, demonstrated that conventional NSAIDs cause clinical relapse within a few days of ingestion in 17−18% of asymptomatic patients with IBD. Patients who tolerate NSAIDs for a week did not seem to be at serious risk for clinical relapse. Another study contacted by Meyer et al. [6] reviewed retrospectively the records of IBD patients, including those with CD, UC, and indeterminate colitis cases examined at an outpatient clinic. The authors showed that the use of NSAIDs was associated with relapse. Previous case−control studies showed that treatment with NSAIDs increased the risk of a new relapse of IBD [25] and of subsequent flares [26]. Bonner et al. [27], in a prospective study, found that the administration of high doses of NSAIDs was associated with a higher numerical Disease Activity Index score among CD patients with colonic involvement, but this was not reflected by an increase in significant disease deteriorations. In contrast, in this study, the use of low-dose NSAIDs was not associated with an increase in disease activity for either CD or UC patients. A case−control study, which included 60 patients with IBD and 62 with irritable bowel syndrome (IBS)

receiving NSAIDs demonstrated that at least 31% of all the IBD patients who used NSAIDs had onset or an exacerbation of IBD, whereas in only 2% of the IBS population who used NSAIDs had an apparent provocation of their disease [26]. Thus, they suggested that patients with a history of IBD should avoid using NSAIDs whenever possible. A large prospective study with 319,465 patients from January 1989 till December 1993 showed that the use of NSAID results in a higher risk of admission to hospital for colitis due to IBD [25], mainly among patients with no previous history. In marked contrast, two studies done by Bonner et al. show that use of NSAIDS in outpatient clinics with active or in remission CD and UC was not associated with a higher likelihood of active IBD [15] and that the use of low-dose NSAIDs was not associated with an increase in disease activity for outpatients with either CD or UC [16]. To elucidate the nature of these associations, more studies should be carried out using a broader spectrum of cases of colitis encountered in clinical practice.

Are COX-2 inhibitors safe in patients with IBD?

Coxibs, selective COX-2 inhibitors, were produced on the hypothesis that they lack the side effects of conventional NSAIDs on the GI tract. Studies of the use of coxibs in IBD patients to date have yielded contradictory results [3], and intestinal toxicity of COX-2 inhibitors in subjects with a normal or inflamed gut has not yet been fully assessed [13, 28]. A retrospective study, which included 27 patients with CD, UC, or pouchitis, showed that COX-2 inhibitors may be safe and beneficial in patients with IBD, as aggravation of the disease was observed in only two patients [29]. Another large prospective, placebo-controlled, double-blind study of 222 patients with UC in remission, who suffered from nonspecific arthritis, arthralgia, or other conditions amenable to NSAIDs drug therapy, demonstrated that therapy with celecoxib for up to 2 weeks did not have a greater relapse rate than placebo in patients with UC in remission [30]. The same conclusion was reached in another multicenter, double-blind placebo-controlled study by Miedany et al. [31], which included 76 patients suffering from IBD who received etoricoxib 60–120 mg/day for 3 months versus 70 patients who received placebo. Etoricoxib therapy was safe and beneficial in most IBD patients and was not associated with exacerbation of the underlying IBD. An open-label trial of the selective COX-2 inhibitor rofecoxib in IBD patients with peripheral arthritis and arthralgia was made by Reinisch and his group [32], and a safety and efficacy profile of rofecoxib was found.

On the other hand, reports on the use of COX-2 inhibitors in IBD patients have suggested a low incidence of disease relapse [10] that quickly ameliorated after withdrawal of the medication. Patients with active IBD and excessive use of COX-2 inhibitors were found to have deterioration of their disease whether it was quiescent disease do not [10]. Wilcox et al. [33] reported three cases receiving rofecoxib, and two of them developed de novo colitis and one exacerbation of IBD. Gornet et al. [13] reported severe exacerbation of CD in a patient treated with rofecoxib and suggested that COX-2 inhibitors are proinflammatory in human IBD. This suggestion could be in accordance with the observations that COX-2 expressed in colonic epithelial cells when the mucosa is inflamed exerts a protective role [34], and inflammatory mediators have a negative regulatory effect on COX-2 expression in colonic epithelial cells [35]. Another open-label study assessed the efficacy and safety of rofecoxib in UC and CD patients with associated arthralgia and controls. Rofecoxib appears to control arthralgia in almost two thirds of IBD patients, but side effects requiring drug withdrawal were observed in almost one quarter of patients [36]. Goh et al. [37] reported an IBD relapse and cytomegalovirus (CMV) infection in a patient with UC while the patient was being treated with rofecoxib. They suggested that rofecoxib may have triggered the relapse and altered the gut permeability to allow CMV colonization and infection, but whether this association was causal or coincidental is unknown.

The use of the selective COX-2 inhibitors may be safer than conventional NSAIDs in patients with clinically inactive IBD, although further controlled trials are required in order to address this issue [36]. On the other hand, COX-2 inhibitors, in addition to their anti-inflammatory effects, seem to exert a chemopreventive activity against colorectal carcinomas arising from UC, and therefore, they could be more attractive candidates for prevention due to their safer profile [38].

Table 1 a literature review of studies evaluating the use of NSAIDs and COX inhibitors in patients with a history of IBD.

Suggested mechanisms of actions of NSAIDs and Coxibs in IBD relapse

NSAIDs

Various pathogenetic mechanisms have been suggested to be involved in the development of gut lesions from NSAIDs. A model suggested by Thiefin and Beaugerie proposes that the main pathogenic steps of the NSAIDs effect on intestinal mucosa include the increase of mucosal permeability that leads to inflammation, ulceration, bleeding, and gut perforation [39].

The major side effects of NSAIDs on the GI include ulceration and bleeding. These drugs are organic acids, and

Table 1 Opinions in articles concerning the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX) inhibitors in patients with inflammatory bowel disease (IBD)

Statements	Articles in favor	Articles against	Ambivalent
Conventional NSAIDs cause exacerbation of IBD	Takeuchi et al. [4] Meyer et al. [6]		
	Evans et al. [25]	Bonner et al. [15]	
	Felder et al. [26]	Bonner et al. [16]	
	Bonner et al. [16]		
Conventional NSAIDs cause de novo IBD	Bjarnason et al. [19] Puspok et al. [18]		
Selective COX-2 and COX-1 inhibition are well-tolerated in the short term	Takeuchi et al. [4]		
COX-2 inhibitors are safer in patients with IBD than NSAIDs	Bonner et al. [10]		
	Mahadevan et al. [29]	Wilcox et al. [33]	Biancone et al. [36]
	Sandborn et al. [30]	Gornet et al. [13]	Reinisch et al. [32]
	Miedany et al. [31]	Bonner et al. [10]	Goh et al. [37]
Concomitant use of NSAIDs and corticosteroids in IBD requires careful follow-up	Biancone et al. [36]		

there is interplay between their respective lipophilic and acidic properties that underlie their GI ulcerogenicity [40]. On the other hand, they also inhibit the COX-1 and COX-2, both of which are involved in the pathogenic process by reducing prostaglandin production that is implicated in the frequent and early clinical relapse of quiescent IBD [4]. Active immunization of rabbits against prostaglandins E2, F2a, and D2 was followed by the development of intestinal ulcers [41]. Another experimental study, using an animal model of dextran sulphate sodium (DSS)-induced colitis, showed that inhibition of both COX-1 and COX-2 and the resulting dramatic decrease in the intestinal level of prostaglandin E(2) was responsible for the NSAID-dependent exacerbation of DSS-induced colitis [42]. Prostaglandins represent one of the most important components of mucosal defense in the colon and are involved from the maintenance of microcirculation and blood flow to the modulation of the mucosal immune system [43]. However, there is evidence that the decrease of endogenous prostaglandin production in the short-term treatment with NSAIDs is not sufficient to alter intestinal permeability or structural integrity [25].

In addition, NSAIDs enhance the intestinal permeability that affects the enterohepatic recirculation and the formation of drug enterocyte adducts [44–46]. The local effect of NSAIDs in the gut mucosa plays a major role in the expression of NSAIDs toxicity. NSAID-induced inhibition of the oxidative phosphorylation causes intracellular adenosine triphosphate (ATP) deficiency that leads to intracellular lesions and the increase in gut mucosa permeability [47]. Bjarnason et al. [48] have suggested that the main underlying mechanism may be the inhibition of the oxidative phosphorylation within enterocytes from high intraluminal levels of NSAIDs after oral use and the increased enterohepatic circulation. This suggestion is supported by studies showing ballooning and vacuolization of enterocyte mitochondria within 1 h after indomethacin administration to rats and changes in the mitochondrial energy production [49].

Small-bowel enteropathy is a common complication of the NSAID use, which leads to occult blood loss or hypoalbuminemia [50, 51]. It has been proposed that the NSAIDs-induced damage to the small intestine is COX independent [50], as transgenic COX-1 knockout mice showed no apparent intestinal pathology and were less sensitive to NSAIDs ulceration [52]. Additional toxicity of NSAIDs in the small bowel occurs with the increase enterohepatic circulation [53]. However, the COX seems to play some part in the pathogenetic mechanisms of small-bowel enteropathy. The COX-dependent mechanisms are important in the mucosal barrier, in its function and repair mechanisms. Indomethacin was found to enhance the small intestinal permeability [46, 54], whereas meloxicam and celecoxib lowered the grade of ulceration [55]. NSAIDs treatment for 6 months induced NSAIDs enteropathy, which lasted for more than a year after cessation [48]. Another mechanism in the pathogenic process is the damage of the intestinal mucosa caused by the contents of the lumen [39]. Data from animal models indicate a role for endotoxin release by translocated bacteria that induces the production of inflammatory mediators, such as interleukin-1 (IL-1), TNF-α, and nitric oxide [25].

Despite the large number of the proposed pathogenetic mechanisms that underlie the action of NSAIDs in IBD, there is little doubt that the ability of NSAIDs to cause injury throughout the GI tract and to exacerbate IBD is mainly due to their ability to suppress prostaglandin synthesis [25, 53].

Coxibs

The Coxibs are a subclass of NSAIDs developed to inhibit selectively COX-2 but not COX-1 based on the hypothesis that COX-2 was the source of prostaglandins E_2 and I_2, which mediate inflammation, whereas COX-1 was the source of the same prostaglandins in gastric epithelium with cytoprotective properties [56, 57]. COX-1 is a constitutively expressed enzyme that is present in all tissues with homeostatic cellular functions. In the GI tract, this enzyme regulates mucosal blood flow, mucus secretion, and acid regulation, and exerts gastric cytoprotection, [3, 58]. In the small intestine and the large bowel, COX-1 is expressed in the lower crypt at equal levels in normal mucosa, and colonic mucosa from CD and UC patients [59]. COX-2 is an inducible enzyme, and its protein is not detected in normal epithelium but in CD and UC in areas of active inflammation, and it is induced by inflammatory mediators in more differentiated cells (i.e., apical epithelial cells) of inflamed mucosa in IBD [34, 60]. The expression of COX-2 in the intestinal mucosa was found to correlate with inflammatory activity in IBD [61]. COX-2 is expressed in a greater amount in colonic mucosa of experimental colitis and colitis in IBD, and it has a beneficial effect in healing experimental colitis [62, 63].

The mechanisms underlying COX-2 inhibitor-induced relapse in IBD are still uncertain, and various hypotheses have been proposed [36]. COX-2 is involved in the inflammatory response in acute and chronic IBD, and increased amounts of prostaglandins correlate with disease activity [61]. Prostaglandins act over a short period; therefore, the cellular distribution of COX-2 is important. COX-2 participates in the regulation of cytokine synthesis and promotes epithelial proliferation and wound healing. Delay in wound healing with COX-2 inhibitors may lead to loss of vasodilatation and increased vascular permeability [64]. Thus, COX-2 inhibition could block the natural process of the inflammatory state that is crucial for wound healing.

Although COX-2 inhibition plays a key role in suppressing the inflammatory process, recent evidence suggests that COX-2 products are involved in maintaining the integrity of intestinal mucosa. Thus, COX-2 inhibitors have an anti-inflammatory action in IBD [65], whereas they affect the regulatory effect of eicosanoids in the intestinal tissue during inflammation [44]. COX-2 inhibitors were found to enhance the inflammation associated with colonic injury in an experimental animal model of colitis [66]. COX-2 was expressed at sites of inflammation and was a major contributor to the prostaglandin synthesis occurring at these sites that lowered the production of reactive oxygen metabolites. COX-2 inhibitors induced greater mortality than standard NSAIDs in the colitic animals, indicating that inhibition of COX-2 may have been the underlying cause of the exacerbation of injury and mortality [66]. Despite their potent extraintestinal anti-inflammatory activity, they had no beneficial effect in trinitrobenzene sulfonic acid (TNBS)-induced experimental colitis [67].

In vitro studies, using colonic biopsies from IBD patients and normal controls indicated that selective COX-2 inhibitors reduced the production of prostanoids, such as PGE2, PGI2 and thromboxane A2, similarly to conventional NSAIDs [68]. Another study using a rat model demonstrated that COX-2 inhibitors reduced PG2 synthesis, whereas they had no effect on thromboxane synthesis [20]. Rofecoxib, in contrast with conventional NSAIDs, was found to have no effect on the small-intestinal permeability, indicating that it causes little or no injury to the GI mucosa [20, 69–71]. However, there is a need for careful follow-up of IBD patients in remission during the first few days of treatment with rofecoxib, as clinical relapse requiring drug

Table 2 Mechanisms of action of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX) inhibitors in patients with inflammatory bowel disease (IBD)

Drug	Mechanism of action
Conventional NSAIDs	COX-1 and COX-2 → PGE reduction
	Surface membrane phospholipid interaction
	Effect on mitochondrial energy metabolism (oxydase phosphorylation inhibition → ATP deficiency → ↑ mucosal permeability)
	Escalation of intestinal inflammatory activity
	Enhancement of enterohepatic circulation
	Formation of drug enterocyte adducts
	COX-independent damage to the small intestine
	Small-bowel enteropathy → blood loss → hypoalbuminemia
	↑TNF-α, IL-1, NO release
	Lower the thromboxane production
COX-1 inhibitors	Impairs mucosal microcirculatory blood flow
	Lower the thromboxane production
	Impair mucous secretion and acid regulation
	Impair renal blood flow and platelet aggregation
COX-2 inhibitors	Immunomodulatory and anti-inflammatory role on the GI tract (selective COX-2 inhibition → PGE reduction)
	Loss of vasodilation
	Increased vascular permeability
	May delay epithelial proliferation
	Delay wound healing
	↑ Oxygen metabolites (LTB4, TNF)
	↑ Leukocyte adherence to the vascular endothelium

PGE prostaglandin E, *ATP* adenosine triphosphate, *TNF-α* tumor necrosis factor alpha, *IL-1* interleukiin-1, *NO* nitric oxide, *GI* gastrointestinal

discontinuation was observed in almost one quarter of patients [36].

COX-2 inhibitors are essential modulators of the intestinal immune response to dietary antigen [24]. There is evidence that selective COX-2 inhibitors may be associated with some GI tolerance due to their selectivity for COX-2, inhibition of COX-1 at only very high doses, and reduced topical irritation [72]. COX-2 inhibitors may affect renal function, inducing salt and water retention [73]. This effect may be worsened by the concomitant use of steroids [36]. Therefore, careful follow-up is necessary of older IBD patients taking both COX-2 inhibitors and steroids, because they are at higher risk of developing both GI and cardiovascular side effects. The risk of a COX-2-selective inhibitors and prednisone is similar to that of traditional NSAIDs. Mechanisms of action of NSAIDs and COX inhibitors in patients with a history of IBD are presented in Table 2.

Conclusion

A large number of people suffering from IBD take NSAIDs for various reasons, as their efficiency in pain control seems to be unquestioned. Some of them experience disease exacerbation. However, the available data remain contradictory and confusing, and it remains uncertain whether COX-2 inhibitors are safer than NSAIDs. In clinical practice, evidence-based decisions for or against NSAIDs in IBD patients are difficult to make due to the variable incidence of IBD and because both types of the anti-inflammatory agents may induce disease recurrence. However, there is some evidence that selective COX-2 and COX-1 inhibition (with low-dose aspirin) appears to be well-tolerated in the short-term treatment [4]. If NSAIDs administration is necessary, there is a need for careful follow-up of IBD patients, mainly those in remission, during the first few days of treatment, as disease aggravation or clinical relapse requires drug discontinuation. Further randomized, double-blind trials should be performed to address this issue [74]. As far as the mechanisms of relapse are concerned, although the reduction of prostaglandins appears to be the hallmark of their adverse effects, more in vitro studies to identify other pathways involved are required.

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