British Journal of Medicine & Medical Research
5(4): 414-426, 2015, Article no.BJMMR.2015.046
ISSN: 2231-0614

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The Association between Cyclo-oxygenase Inhibitor Medications and Clinical Relapse in Inflammatory Bowel Disease: Review of Current Perspectives

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Authors' contributions

This work was carried out in collaboration between both authors. Authors AH and ILPB jointly conceived the study. Author AH performed the initial literature search and data synthesis, wrote the initial drafts of the manuscript and reviewed the final manuscript. Author ILPB coordinated the study, reviewed initial versions of the manuscript and wrote the final version of the paper. Author ILPB is guarantor of the paper. Both authors read and approved the final manuscript.

Article Information

DOI:10.9734/BJMMR/2015/13064
Editor(s):
(1) Mohamed Essa, Department of Food Science and Nutrition, Sultan Qaboos University, Oman.
Reviewers:
(1) Anonymous, Rush University Medical Center, USA.
(2) Ng Zhi Xiang, Department of Biomedical Science, Faculty of Medicine, MAHSA University, Malaysia.
(3) Anonymous, Rush University Medical Center, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=663&id=12&aid=6112

Review Article

Received 31st July 2014
Accepted 29th August 2014
Published 16th September 2014

ABSTRACT

Background: Patients with inflammatory bowel disease (IBD) often have associated conditions which may benefit from treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclo-oxygenase-2 (COX-2) inhibitors. However, evidence has suggested there may be an association between COX- inhibition and relapse in IBD, which leads to clinicians being reluctant to prescribe these agents.
Aims: The aim of this review is to review the possible biological mechanisms, linking NSAIDs and IBD-relapse and current knowledge on the possible association of NSAIDs and clinical relapse in IBD.
Results: IBD relapse due to NSAID use is most likely due to prostaglandin inhibition via dual COX-

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inhibition, although the topical effect of NSAIDs on the intestine may also play a role. The evidence for an association between NSAIDs and IBD relapse is contradictory and generally weak, but it is likely a small percentage of patients relapse when taking NSAIDs, but it is not known which patients are at risk. Mixed results have also been obtained from studies examining COX-2 selective agents; although a single randomized controlled-trial showed that celecoxib is safe in ulcerative colitis in the short term.

Conclusions: At present the data are contradictory and most published studies have serious flaws. Overall the association between use of NSAIDs and IBD-relapse seems rather weak, Cyclo-oxygenase inhibitors should not be withheld from stable IBD patients, if clinically indicated and appropriate cautions and monitoring are used. Celecoxib would seem a sensible first choice. Further studies are needed to help identify which patients are at risk of relapse with NSAIDs.

Keywords: Inflammatory bowel disease; ulcerative colitis; crohn's disease; non-steroidal anti-inflammatory drug; prostaglandins; cyclo-oxygenase.

ABBREVIATIONS

NSAID: Non-steroidal anti-inflammatory drug, PG, prostaglandin, COX: cyclo-oxygenase, IBD: inflammatory bowel disease, LT: leukotriene, TX: thromboxane, UC: ulcerative colitis, CD: Crohn's disease, OR: Odds ratio, 95% CI: 95% confidence intervals.

1. INTRODUCTION

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are a significant health problem. These are common conditions, with an incidence of 24.3 and 12.7 per 100,000 person-years in Europe for UC and CD respectively [1]. The United Kingdom has one of the highest incidences of IBD in the world and it continues to rise [2]. In 2011, it was thought that there were approximately 240,000 patients in the UK with IBD, with UC making up 146,000 and CD 87,000 [3]. Furthermore, it has been reported that IBD is one of the top 5 most expensive GI disorders, with $2.8 billion per year in the US being spent on the disease [4]. With numbers of such magnitude, keeping patients in remission is both beneficial for the patient and the budget of all health services.

Non-steroidal anti-inflammatory drugs (NSAIDs) are readily available over the counter and are frequently prescribed by general practitioners and hospital clinicians. Patients with IBD are likely to use these medications for non-IBD related conditions, such as arthralgia, headache and arthritis, as the general population do. In addition to this, IBD patients are also prone to extra-intestinal manifestations of IBD such as arthralgia, arthritis, sacroilitis and ankylosing spondylitis, with a reported prevalence in IBD patients between 4 and 23% [5]. These are traditionally treated with NSAIDs first line before using drugs such as methotrexate and biologics [6].

The main mechanism of action of NSAIDs is by blocking prostaglandin production through the cyclo-oxygenase (COX) pathway [7]. Prostaglandins (PGs) are mediators of pain, inflammation and fever; therefore NSAIDs are well recognised for their anti-inflammatory and analgesic properties [7]. In addition to these well-known actions of PGs, there are many lesser recognised actions, particularly in the bowel [8-11]. It is possibly due to these that it is thought NSAIDs may exacerbate quiescent IBD [10,12-16].

The association between both selective and non-selective COX inhibitors and relapses in IBD has been an area of interest for researchers for many years [17-19]. Even though much more is now known about this association, the strength and the importance of this association as well as causality remain open to debate and clinicians still face the issue of what to advise IBD patients when they have the need for analgesia and anti-inflammatories in conditions which are traditionally treated with NSAIDs [15]. In 2009, Kefalakes et al. [15] examined the link between NSAIDs and IBD exacerbations and concluded that NSAIDs could be used in IBD patients where necessary, but only with careful follow-up. Which patients are likely to relapse and the mechanisms by which this occurs are still unclear.

The aim of this review is to consolidate the current knowledge on NSAIDs and their

association with exacerbation of inflammatory bowel disease, identifying any flaws in the research and any potential gaps in the understanding of this association. Furthermore, it will examine any possible factors which put IBD patients at risk of relapse with NSAIDs.

2. POSSIBLE BIOLOGICAL MECHANISMS

Arachidonic acid is the precursor for the eicosanoids (that is mediators derived from 20-carbon polyunsaturated fatty acids); these include several families of mediators, predominantly prostaglandin (PG), thromboxane (TX) and leukotriene (LT) families. The polyunsaturated omega-6 fatty acid arachidonic acid is metabolised via three different pathways, the cyclo-oxygenase, the lipoxygenase and the cytochrome P450 pathways [11,20,21]. It is via the COX pathway that prostaglandins are formed, whereas it is currently believed that metabolism of arachidonic acid through the lipooxygenase and cytochrome P450 pathways generally produces non-prostaglandin family mediators: the leukotrienes, lipoxins hydroxyeicosatetraenoic (HETE), epoxyeicosatrienoic acid (EET) and hydroperoxyeicosatetraenic acid (5-HPETE). [11,20,21]. The isozymes COX-1 and COX-2 catalyse the production of PGH2 (prostaglandin H2) from arachidonic acid which is then metabolized by specific prostaglandin and thromboxane synthases to produce PGI2 (prostacyclin), PGD2, PGE2, PGF2 and TXA2 (thromboxane A2) [22]. COX-2 is the inducible form of the enzyme and its expression is up-regulated during inflammation. COX-1 is generally regarded as a constitutive ('housekeeping') non-inducible enzyme with widespread tissue distrubtion.

The lipoxygenase pathway produces leukotrienes from arachidonic acid using 5-lipoxygenase. Leukotrienes, like prostaglandins, are pro-inflammatory molecules and have potent effects on vascular tone and permeability, mucus secretion, and leukocyte recruitment [23]. Studies have shown that colonic mucosae of IBD patients has an over expression of leukotriene B4, and it is thought that 5-amino-salicylates reduce inflammation in IBD partly by inhibiting production of this leukotriene [23].

Metabolism of arachidonic acid via the cytochrome P450 pathway produces hydroxyeicosatetraenoic acid and epoxyeicosatrienoic acid, the 5-HETE is a precursor for leukotrienes as well as playing a role in processes such as cellular proliferation, apoptosis, inflammation, and haemostasis [24].

Metabolism of arachidonic acid via the 15-lipoxygenase pathway produced lipoxins A and B which are thought to have predominantly anti-inflammatory actions, whilst a separate family of anti-inflammatory 'non-classical eiscosanoids,' the resolvins and protectins are formed from the 20-carbon omega-3 polyunsaturated fatty acid eicosapentaenoic acid and docosahexaenoic acid via the actions of acetylated COX-2 and 5- and 15-lipoxygenase [25,26]. Surprisingly little is definitively known about these mediators in IBD and the relationships with NSAIDs and other COX-pathway inhibitors, but this does illustrate the complexity of the potential pro- and anti-inflammatory pathways generated from polyunsaturated fatty acids and why the interactions with, and the effects of NSAIDs may be so variable in clinical studies [27].

2.1 Inhibition of Prostaglandin-mediated Cellular Actions in the Colon

Prostaglandins are found throughout the body, both in the central nervous system and peripheral tissues and have paracrine and autocrine functions. The normal colon synthesizes PGI2, PGE2, PGD2, PGF2α, and TXB2 [10,11] However in IBD, the production of prostaglandins increases and this is proportional to the severity of disease activity [10]. COX-2 expression is upregulated to a greater degree than COX-1, [28,29] with a significant increase in PGE2, PGI2 and TXA2 in inflamed colon compared to healthy colon [30].

In the healthy colon, prostaglandins are involved in many physiological processes, such as mucus production, vasodilatation, inflammation, cytoprotection, cell proliferation and epithelial barrier function. The role of prostaglandins in IBD pathophysiology can be linked to these processes.

2.1.1 Mucus production

The gastrointestinal tract, including the colon, produces mucus to lubricate and protect the mucosa from bacterial invasion [31]. Prostaglandins are known to have a role in mucus secretion, and this has been seen in both healthy and inflamed colons [10,32,33]. The mucus layer prevents contact between the luminal bacteria and the epithelium, and in IBD it

is thought that there is a decrease in mucus and breaks in this layer lead to bacterial adherence and invasion [31].

If taking NSAIDs affects mucus production in the colon through prostaglandin inhibition, this could explain a relapse in symptoms in stable IBD patients. Further research looking at the effect of NSAIDs on mucus secretion in IBD patients would be beneficial to understand this association.

2.1.2 Vasodilatation

PGD2 has been shown to act with acetylcholine to maintain perfusion to inflamed colonic tissue in patients with IBD [34]. It is thought that this occurs by a unique mechanism where prostaglandins are produced from the arteriolar media and adventitia, not in the epithelium as in the healthy colon [34]. In addition to this, the increase of PGD2 via increased COX-2 activity allows vasodilatation to occur when acetylcholine is diminished in IBD [34]. This proposed mechanism of vasodilatation in IBD could be compromised if a patient then used NSAIDs.

However, further work needs to be done in this area as this study was only carried out on patients with severe disease and it is not known if this mechanism continues when a patient is then in remission.

2.1.3 Cell proliferation

PGE2 has been shown to trans-activate epidermal growth factor receptor (EGFR), which is responsible for cell proliferation and is key for repairing and maintaining the integrity of the gastrointestinal mucosa [11]. Furthermore, this mechanism has been implicated in both ulcer healing and carcinogenesis throughout the length of the gastrointestinal tract [8, 9,11].

It is widely known that NSAIDs impair ulcer healing in gastro-duodenal mucosa [35], and this is also true for colonic ulcers. The reason why NSAIDs delay ulcer healing in IBD is likely due to prostaglandin inhibition causing interference with EGFR and cell proliferation [11].

2.1.4 Inflammation

Prostaglandins are mainly typically known for their pro-inflammatory properties, as they are mediators of the cardinal signs of inflammation (redness, swelling, pain and heat). Due to this, COX-inhibition is normally associated with anti-inflammatory actions and using this reasoning, it could be argued that COX-inhibitors may actually be beneficial for IBD.

However, prostaglandins also have anti-inflammatory properties. For example PGE2 has anti-inflammatory actions on innate immune cells, such as neutrophils, monocytes, and natural killer cells [36]. Additionally, products of COX-2 have been implicated as having a role in the resolution of inflammation; however all these products have not yet been fully identified [36,37]. It has been noted that PGD2 expression is up-regulated in UC patients in remission, suggesting that this plays a role in long-term resolution and control of inflammation [38].

The research into the anti-inflammatory effects of prostanoids is on-going, and current thinking is that the same prostanoids could have an opposite effect depending on its location, target tissue and the type of prostanoid receptors expressed [37]. The increase in COX-2 and the resulting increased prostaglandins seen in IBD may contribute to down-regulation of inflammation. This could theoretically lead to a relapse in symptoms when NSAIDs are used.

Furrer and Moreno speculated that the use of NSAIDs blocks the formation of prostaglandins, forcing arachidonic acid metabolism down the lipo-oxygenase and cytochrome P-450 pathways [11]. They suggested that this could hypothetically cause an increase in eicosanoids such as leukotrienes and 5-HETE which are proinflammatory and also cause impairment of barrier function [11]. This could also be an explanation of how NSAIDs have a harmful effect of IBD.

2.1.5 Epithelial barrier

Prostaglandins are involved in the function of the epithelial barrier in numerous ways. Healing and restitution of the epithelium (section 2.1.3) and enhancement of vasodilation and contribution to the development of inflammatory exudate (sections 2.1.2 and 2.1.4) have already been discussed. In addition to these roles, PGs are also involved in the permeability of the epithelial barrier.

Although the pathogenesis of IBD is not yet fully understood, it is known that defects in the mucosal barrier allow the continuous stimulation of the immune system via bacterial translocation

and penetration. It is thought that PGE2 synthesis is involved in the regulation of intestinal paracellular permeability and therefore regulates the epithelial barrier [11,39]. Research has shown that NSAIDs disrupt epithelial barrier function, probably due to PGE2 reduction, and this may exacerbate IBD [40].

2.2 Topical Effect of NSAIDs

As well as inhibition of prostaglandins, there are other potential ways in which NSAIDs can exacerbate IBD based on the topical effect of the NSAID. Primarily it is thought they behave like a detergent due to their lipophilic and acidic properties, which disrupt the mucus layer and/or the cell membrane [41,42]. Another theory is that uncoupling of mitochondrial oxidative phosphorylation leads to a disruption in the epithelial barrier function due to an inability of mitochondria to produce enough ATP [42]. This leads to a dysfunction in the intercellular junctions and an increase in permeability of the mucosa, allowing bacteria to enter.

NSAIDs undergo enterohepatic circulation, where the drug is re-circulated through the small intestine and the liver. This repeatedly exposes the small intestine to the NSAID, potentially exacerbating any topical effect the NSAID causes [43]. However, there is no published evidence to show that NSAIDs reach the lumen of the colon, so it is unlikely that any topical affect NSAIDs have attributes to colonic IBD.

2.3 Summary of Possible Mechanisms Linking Cyclo-oxyganse Inhibitor Treatment and Relapse of IBD

In summary, the plausible biological mechanisms for NSAIDs causing IBD relapse are likely due to endogenous prostaglandin inhibition in the colon. The increase in prostaglandins seen in IBD is diminished by ingesting COX-inhibitors which possibly leads to a relapse in symptoms. Prostaglandins are involved in many physiological processes in the colon, therefore the mechanism by which relapse occurs is most likely to be multifactorial. The anti-inflammatory properties of PGE2 and involvement of PGD2 in the resolution of inflammation may be diminished due to NSAID use. The topical effect of NSAIDs may also play a part in causing relapse in proximal small bowel Crohn's disease. Further research is needed in the aforementioned areas to further our knowledge on this topic.

3. EPIDEMIOLOGICAL EVIDENCE FOR IBD-RELAPSE ASSOCIATED WITH NON-SELECTIVE COX-INHIBITORS

3.1 Non-selective COX-inhibitors

The association was first noted between use of agents that inhibit the cyclo-oxygenase enzymes and IBD relapse in the 1980s [17,44]. These case reports showed that NSAIDs caused relapse in particular patients but this needed to be backed up by larger population based studies [10].

Evans et al. carried out a case-control study in 1997 to compare NSAID use between emergency admissions for IBD and matched community controls [45]. The study examined 200 patients admitted for IBD and 1198 community controls matched for age and sex. It was found that there was an association between current and recent NSAID use and emergency admissions for IBD. The odds ratios (adjusted for exposure variables) for current and recent NSAID use associated with a relapse of IBD overall was 1.12 (95% confidence interval (CI) 0.48-2.59) and 1.59 (95% CI 0.79-3.19) respectively for CD and 1.72 (95% CI 0.62-4.79) and 1.96 (95% CI 0.81-4.75) for UC [42]. Although this association was noted, the difference was not statistically significant.

This study's strengths are in the relatively large (by comparison) sample size and the use of dispensing records to estimate NSAID use. However, it is limited by the fact any medications purchased over the counter were not included and not all medicine dispensed is taken by the patient. Furthermore, by using emergency hospital admissions as a definition for the cases, this eliminated any patients who have a worsening of symptoms not warranting an emergency department visit.

Bonner et al. [46] also carried out a case-control study but used inactive IBD as a control group. 192 patient records (112 CD and 90 UC patients) were retrospectively reviewed from a single gastroenterologist's IBD patients for NSAID use. As this was a retrospective study a disease activity score could not be completed, so clinical impression was used to categorise the patients as active or inactive. The results from this study showed that NSAID use had no association to active disease, with the odds ratios of 0.34 (95% CI 0.07-1.39) for CD and 0.65 (95% CI 0.15-3.31) for UC [46].

These authors discussed the concept that not all patients with IBD are equally susceptible to relapse due to NSAIDs [46]. However, they did recognise the limitations of their study, discussing the issue that the severity of disease was not accounted for and that some of the patients had been previously warned not to use NSAIDs so this could have biased the results [46]. Furthermore these results have to be interpreted without the knowledge of whether these patients have relapsed, have chronically active disease or new-onset IBD.

A further case-control study was carried out by Felder et al. matching 60 IBD patients to 62 controls with irritable bowel syndrome (IBS) [47]. NSAID use was quantified by using a questionnaire in an interview with both populations. In those who had used NSAIDs in the last month they reported an odds ratio of having an exacerbation or new onset IBD compared to IBS as 20.3 (95% CI 2.6-159.7) [47]. This odds ratio should be interpreted with caution due to the small sample sizes, comparison with irritable bowel patients rather than other IBD patients, the wide confidence interval and the assumptions made by the authors about the direction of the correlation between NSAIDs and IBD.

The major flaw in this study is the choice of control group. IBS is a condition that is associated with chronic pain and the data from this paper shows that 100% of the control group used NSAIDs at some point in the study period, and 92% used NSAIDs for greater than one month before interview [47]. This group of patients who are such regular chronic users of NSAIDs were not an entirely appropriate choice of control subjects for such a study, as not only had they clearly selected a group of "NSAID-tolerant' uses as a control group but this studied stated that its "main focus" was to compare usage only "during the month before symptoms" [47]. Only a maximum of 8% of the control group would have been able to have specifically only used NSAIDs in the last month, and this has affected the odds ratio.

Forrest et al. conducted a systematic review on this topic in 2004 and concluded that the epidemiological evidence was mostly limited due to small sample sizes and poor methodology [48]. Furthermore it was suggested that the epidemiological evidence available at the time for an association of NSAIDs with IBD was "weak" and recommended that a prospective cohort study would be beneficial [48]. The authors felt that from this review there was not enough evidence to prevent IBD patients from taking NSAIDs for rheumatological complaints and that the data was not amenable to meta-analysis due to the wide variation in methodologies used.

Following this review, a prospective open-label trial was published. Takeuchi et al. designed a study which followed 209 stable IBD patients for 4 weeks while they were taking NSAIDs [14]. The study participants were split into groups and 26 patients were given paracetamol (which acted as a non-NSAID control), 32 given naproxen, 29 given diclofenac and 22 given indomethacin. The other 100 patients were divided into 5 equal groups and given paracetamol, naproxen, nabumetone, nimesulide or aspirin. The second part of this study aimed to assess the possible mechanism of relapse by administering medications that had different mechanisms of action. Disease activity was monitored both by the Harvey-Bradshaw clinical disease activity index and faecalcalprotectin levels. The authors used the Harvey-Bradshaw index for both CD and UC patients.

The results of this study found that 17%-28% of patients relapsed while taking NSAIDs, with naproxen and indomethacin both with statistically significant p-values compared to the control ($p=0.01$, 0.08 and 0.04 respectively) [14]. The second part of the study found that the number of patients that relapsed while taking naproxen and nabumetone differed significantly ($p<0.01$) to those taking paracetamol, nimesulide and aspirin [14]. From this the authors concluded that most IBD patients do not relapse when taking NSAIDs but up to 30% relapse within a week of NSAID ingestion. Furthermore, they explain that nimesulide and low-dose aspirin seem to be tolerated in IBD patients and these could be used for appropriate indications [14]. Their data suggests that dual inhibition of the COX isozymes is responsible for clinical relapse, rather than just COX-1 or COX-2.

The strength of this study is its prospective design which allows the elimination of any recall bias and a directional association to be made. However, the use of the Harvey-Bradshaw index to measure disease activity has only been validated for CD and not UC, so is not an appropriate tool for UC patients. The authors do not seem to have made any adjustments or considerations towards the smoking habits of the patients, which could be a major confounder. In

addition to this, it is not known whether the patients were randomly allocated to each group or whether they were picked to take each medication, which could lead to selection bias.

Meyer et al. [49] published another case-control study in 2006 using IBD patients in remission as the control group, similar to the study design of Bonner et al. [43] This study also used a retrospective records review to obtain information on medication use and disease activity and included the records of 60 patients. The authors reported that 22 patients were in relapse and 38 were in remission. Of these, 9 in relapse and 10 in remission had used NSAIDs in the past month, giving an odds ratio of 6.31 (95% CI 1.16-34.38) which was adjusted for age, gender and maintenance therapy [49].

Although this study aimed to collect information on smoking habits, it only managed to do so for 15% of patients, thus this data could not be used to adjust the statistical analyses. Furthermore, the authors note that a limitation to their study is a lack of information on over-the-counter NSAIDs, as it was unlikely for these to be recorded in a patient's notes. With a relatively small sample size and no calculation to estimate power, these results should be interpreted with this in mind.

Overall, although there are data available on the topic of non-selective NSAIDs causing IBD relapse, in general the results are conflicting and most study designs suboptimal. However, as it has been noted previously, there is no one definitive epidemiological study that has been carried out with precision that has given definite answers on the matter. Table 1 identifies the relevant studies that have been carried out and shows that an equal number of studies show an association to those that do not, with varying odds ratios. The studies are too heterogenous in design and analysis to accurately subject to a meta-analysis

3.1.1 Summary of associations between non-selective COX-inhibitors and IBD-relapse

It is likely that non-selective NSAIDs do cause relapse in some IBD patients, probably a small proportion. At present it is unclear how common NSAID-induced relapse really is, and if any particular members of the drug class are more commonly implicated. It is also unclear if any patient- or coincidental treatment-related factors influence the risk of drug-related relapse. There is some evidence that NSAIDs that inhibit both COX-1 and COX-2 are more likely to cause relapse. Further research is needed which includes adjustment for tobacco smoking and has more detailed information on over the counter medicines. One way this could be done is by using both patient interviews and record reviews, to ensure accurate information is obtained.

Table 1. Results of epidemiological studies examining the association of non-steroidal anti-inflammatory drugs (NSAIDs) and relapse in inflammatory bowel disease (IBD) patients

Author	Study design	Control group	Odds ratio (95% CI)	Association reported between NSAIDs and relapse
Evans (1997) [45]	Case-control	Community controls	1.59 (0.79-3.19) CD 1.96 (0.81-4.75) UC	No
Bonner (2000) [47]	Case-control	Inactive IBD	0.34 (0.07-1.39) CD 0.65 (0.15-3.31) UC	No
Felder (2000) [48]	Case-control	IBS†	20.3 (2.6-159.7)	Yes
Meyer (2006) [50]	Case-control	Inactive IBD	6.3 (1.16-34.38)	Yes
Takeuchi (2006) [14]	Open-label	IBD paracetamol users	‡	Yes

† IBS - irritable bowel syndrome. Flawed methodology in this paper led to a larger than expected odds ratio, ‡ No odds ratio reported due to open-label study design

3.2 Selective COX-2 inhibitors

Selective COX-2 inhibitors were designed and manufactured as the advanced generation of NSAIDs. Those that would not cause the traditional (mainly upper) gastrointestinal side effects that are due to COX-1 inhibition [50,51]. Since then, the use of selective COX-2 inhibitors for rheumatological conditions has been successful and these drugs are now used commonly by patients for arthritis, gout and arthropathies. However, their use has been limited by the concern over the cardiovascular side effects which led to the withdrawal of rofecoxib and valdecoxib from the market [52].

In IBD the colon increases expression of the inducible COX-2 enzyme. This produces the pro-inflammatory effects associated with prostaglandins, but as previously mentioned this increase in COX-2 may also be a protective mechanism due to the lesser well known anti-inflammatory properties of the prostanoids produced. The effect of selective COX-2 inhibitors on IBD was first tested in animal studies which produced contradictory evidence. A study by Singh et al. exposed rats with chemically-induced IBD to celecoxib and noted worsened inflammation and a reduction of PGE2 levels [53]. On the other hand, Kankuri et al. showed that nimesulide reduced inflammatory oedema in chemically-induced IBD in rats by reducing PGE2 levels [54].

In vitro human studies showed that a highly selective COX-2 inhibitor (L-745 337) inhibited PGE2 in IBD colon biopsies to the same extent as indomethacin (a traditional non-selective COX inhibitor). The authors recommended that selective COX-2 inhibitors should be treated with the same caution as non-selective NSAIDs [30]. This led to a number of clinical and epidemiological studies being carried out to observe the safety of selective COX-2 inhibitors in IBD.

Mahadevan et al. [55] conducted a retrospective case review of all IBD patients who had been taking celecoxib and rofecoxib in 3 gastroenterology practices. Out of the 27 patients who were taking selective COX-2 inhibitors, two patients experienced a relapse of IBD and both patients saw their IBD symptoms reduce upon discontinuing rofecoxib [55]. The authors suggested that their results showed that COX-2 inhibitors were safe to use in IBD patients. This study was undertaken on relatively few patients and as the authors rightly state a prospective placebo controlled trial was needed to further establish the safety.

A prospective open-label study was undertaken in 2003 looking at the efficacy of rofecoxib in IBD-related arthropathies [56]. Thirty two patients with stable IBD were given rofecoxib as treatment for arthropathy or arthralgia and were followed for 20 days where any adverse events were reported. The authors concluded from the Crohn's disease activity index (CDAI) scores that no flares of IBD occurred in this study, and in fact a significant improvement was seen due to an increase in general well-being ($p<0.001$) [56]. However, they do report two CD patients discontinuing the drug due to diarrhoea and bleeding from a perianal fistula.

The strengths of this study are that it is prospective in nature and it is known that eight of these patients have previously had exacerbations after using non-selective NSAIDs [53]. However, it seems apparent that two patients did possibly have a flare-up of IBD symptoms, even if their CDAI scores did not change considerably. This needs to be taken in to consideration.

Another open-label trial looking at the safety of rofecoxib in IBD showed conflicting results. Biancone et al. [57] assessed 45 inactive IBD patients with the same dosage but also had a control group of thirty dyspeptic patients. They found that 20% of IBD patients had to withdraw from rofecoxib use due to clinical relapse compared to 3% of the control group. This was a statistically significant difference with a p value of <0.001 [57]. The authors explain the variation in their results to Reinisch et al. [53] could be due to the difference in characteristics between the two study populations.

The results from Biancone et al. were backed up with a retrospective records review undertaken in 2004. This study of only 33 patients showed that 39% of patients taking rofecoxib or celecoxib had an IBD exacerbation between 3 days and 6 weeks of commencing therapy [58]. Of the patients that relapsed, 38% had resolution of symptoms solely by withdrawing the drug. This study, undertaken by Matuk et al. [58]. also reported that COX-2 related exacerbations IBD were not related to of age, disease type or location or the use of immunosuppressants for IBD.

The authors explored reasons why the incidence of exacerbation was higher in their study than in the previous studies: explaining this could possibly have been due to the underestimation of IBD patients using selective COX-2 inhibitors in the first instance, which then led to a falsely high incidence for exacerbation in this smaller population. Although the relapse rate was high in this population, this study included a very small sample size and is limited by the retrospective design and subjective definition of relapse.

The first randomized double-blinded placebo-controlled trial of celecoxib in ulcerative colitis was carried out by Sanborn et al. in 2006 [59]. This pilot trial randomly assigned 222 UC patients in remission to receive celecoxib at a dose of 200mg or a placebo for 14 days with a ratio of 1:1. The study showed that exacerbation of UC occurred in 3% of patients taking celecoxib (95% CI 0.6-7.8%) and in 4% of patients taking the placebo (95% CI 1.3-6.5%), which was not a significant difference between groups (p=0.719) [56]. In addition to this, the withdrawal rate and reporting of adverse events were also not significantly different between the two groups (p=0.08 and p>0.20 respectively).

The advantage of this study is that it is a placebo controlled prospective study that allows a causative association between celecoxib and UC relapses to be established. The authors took care to ensure adequate randomisation and a sufficient sample size. However this study does have limitations as it only included UC patients who were taking 5-aminosalicylates (5-ASAs) and /or azathioprine and only gave celecoxib for a short period of time. Therefore the results of this study cannot be generalised to all cases of IBD and should be interpreted taking this into consideration.

3.2.1 Summary of associations between selective COX-2 inhibitors and IBD-relapse

Overall, the data examining the association between selective COX-2 inhibitors and IBD relapses have expanded with time but much of this evidence is contradictory, as shown in Table 2, and based on small, uncontrolled studies or with questionable comparators and overall there do not seem to be sufficient data to avoid the use of COX-2 inhibitors in IBD. However, the strongest evidence against COX-2 inhibition causing a relapse in IBD (specifically the use of celexocib in ulcerative colitis) has been provided by the Sandborn study [59]. This is the single (albeit short-term) randomized controlled trial. This study has given some clarification on the topic, but the results may not be particularly generalisable to Crohn's disease or longer-term treatment. Currently, it is seems that celecoxib is safe to use in UC patients who are in remission taking 5-ASAs and/or azathioprine. Future work should be prospective and controlled in nature and should concentrate on the safety of selective COX-2 inhibitors in CD and in UC patients who are not taking the aforementioned medications [59]. There certainly does not seem to be enough data to preclude the use of celecoxib, if indicated, along with appropriate monitoring and patient consent.

Table 2. A summary of the results of studies examining the association of selective COX-2 inhibitors and relapse in inflammatory bowel disease (IBD) patients

Author	Study design	Type of IBD	Control group	Relapse rate #	Association reported between COX-2 inhibitors and IBD relapse
Mahadevan (2002) [55]	Retrospective records review	CD & UC	None	7.4%	No
Reinsch (2003)	Open-label	CD & UC	None	No relapses	No
Biancone (2004) [57]	Open-label	CD & UC	Dyspepsia	20%	Yes
Matuk (2004) [58]	Retrospective records review	CD & UC	None	39%	Yes
Sandborn (2006) [59]	Randomized controlled trial	UC	Placebo	Celecoxib 3% Placebo 4%	No

 # % of patients who relapsed during the study while taking a selective COX-2 inhibitor

4. CONCLUSION

NSAIDs and selective COX-2 inhibitors can be valuable medications for IBD patients who frequently suffer with arthralgia and/or arthropathies or have coincidental problems for which anti-inflammatory medication can be helpful [6]. However many clinicians currently warn patients against their use in fear of causing IBD relapse, potentially limiting treatment option for patients.

There is biological plausibility and experimental data showing that COX-inhibition can be both beneficial and deleterious in colitis. The biological mechanisms linking IBD-relapse and COX-inhibitor use are complex: but is most likely that dual inhibition of both COX-enzymes reducing endogenous prostaglandin production in the intestine plays a central role in inducing any relapse [9,14,60]. There is some evidence that anti-inflammatory COX-1 activity is mostly involved in the early stages and COX-2 in later phases of the inflammatory response in animal models [61]. A recent study involving animal colitis models has suggested that PGE2 is protective due to its modulation of pro-inflammatory cytokines in IBD, and by simultaneously inhibiting both COX-1 and COX-2, a clinical relapse may be induced [60]. In addition, NSAIDs may also exert a topical effect on the small intestine due to uncoupling of mitochondrial oxidative phosphorylation and their lipophilic properties causing disruption of cell membranes [42].

Epidemiological evidence for an association between NSAIDs and IBD relapse is contradictory, generally of poor quality and somewhat perplexing, with many of the previously published studies containing serious methodological flaws, having generally small sample sizes, having used very subjective definitions of relapse and disease activity and/or being retrospective in nature [48]. The variability in the evidence available makes it exceptionally difficult for a clinician to base their practice on the information it provides. Prospective cohort studies and randomized double blinded controlled studies which adjust for smoking and include information on over-the-counter NSAIDs are needed to strengthen the evidence base.

In addition to the evidence on traditional NSAIDs, research into the safety of selective COX-2 inhibitors in IBD has also shown a wide disparity in results. However, the study with the soundest methodology shows that celecoxib does not seem to cause a significant increase in relapses in stable patients with UC, at least in the short-term [59]. Further studies with a similar design are needed to observe selective COX-2 inhibitor use in CD.

It is most likely that NSAIDs and COX-2 inhibitors do cause symptomatic relapse in a small percentage of IBD patients, but evidence shows the majority of patients remain in remission. It has yet to be ascertained if certain patients are more at risk of relapse. It would be helpful to identify patient-, disease- and drug-related effects that were associated with relapse. This would permit this subset of patients to use NSAIDs and selective COX-2 inhibitors safely, allowing patients to reap the benefits of these useful medications. A well designed long-term prospective cohort study or large case control study which identifies known risk factors such as smoking and collects information on other possible factors (such as co-morbidities, concurrent medications and disease severity to mention a few) is needed to help identify if certain patients are prone to relapse when using COX inhibitors.

At present, we feel that given the uncertainties over the absolute risk of relapse, if a cyclo-oxygenase inhibitor is clinically indicated in a stable IBD patient, then it should not be regarded as contraindicated because of the possibility of relapse. A selective COX-2 inhibitor (most specifically celecoxib, on which the published data concentrate), would seem the most sensible choice in this situation, with appropriate counselling and clinical review of the patient.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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