REVIEW

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Potential Strategies in the Prevention of Nonsteroidal Anti-inflammatory Drugs-Associated Adverse Effects in the Lower Gastrointestinal Tract

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With the increasing use of nonsteroidal anti-inflammatory drugs (NSAIDs), the incidence of lower gastrointestinal (GI) complications is expected to increase. However, unlike upper GI complications, the burden, pathogenesis, prevention and treatment of NSAID-associated lower GI complications remain unclear. To date, no cost-effective and safe protective agent has been developed that can completely prevent or treat NSAID-related lower GI injuries. Selective COX-2 inhibitors, misoprostol, intestinal microbiota modulation, and some mucoprotective agents have been reported to show protective effects on NSAID-induced lower GI injuries. This review aims to provide an overview of the current evidence on the prevention of NSAID-related lower GI injuries. **(Gut Liver 2020;14:179-189)**

Key Words: Anti-inflammatory agents, non-steroidal; Lower gastrointestinal bleeding; Protective agents

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit mucosal prostaglandin production, could induce both upper and lower gastrointestinal (GI) mucosal damages.[1] In the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) trial, NSAIDs use was associated with a higher risk of upper GI bleeding (relative risk [RR], 2.6; 95% confidence intervals [CI], 2.0 to 3.5) than lower GI bleeding (RR, 1.4; 95% CI, 1.0 to 1.9).[2] However, lower GI events still accounted for 40% of all NSAID-related serious GI events.[3] With the increasing use of gastroprotective agents as well as the declining prevalence of *Helicobacter pylori* infection, the incidence of upper GI complications is generally decreasing but the incidence of lower GI complications is rising.[4,5] Many of the lower GI complications are related to the use of NSAIDs and aspirin. Even with the concurrent use of gastroprotective agents, up to three-quarters of patients using NSAIDs could still suffer from small intestinal injuries.[6] However, unlike upper GI complications, the burden, pathogenesis, prevention and treatment of NSAIDs-associated lower GI complications remain unclear.[7] To date, there is no evidence-based effective and safe strategy that can completely prevent or treat NSAIDs-related lower GI injury.[7,8] This review aims to give an overview of the current evidence of potential strategies in the prevention of NSAIDs-related lower GI injury. Details of all studies are presented in Table 1.[9-45]

SELECTIVE COX-2 INHIBITORS

Selective COX-2 inhibitors, with its selectivity on COX-2 inhibition, is one of the major candidates to replace nonselective NSAIDs in reducing the risk of GI injury. Although it has been widely studied in the prevention of upper GI complications,[12,46-48] evidences supporting the benefits of selective COX2 inhibitors over nonselective NSAIDs in the lower GI tract were limited.

It was suggested that use of selective COX-2 inhibitors was associated with a reduced incidence of GI perforations, ulcers and bleeds, with less fecal blood loss and fewer endoscopically detectable lesions.[49] Hawkey *et al*.[10] compared the small-bowel injury of selective COX-2 inhibitor, lumiracoxib, with naproxen and placebo in a double-blind randomized controlled trial (RCT). They found that acute small-bowel injury induced by lumiracoxib is less frequent than with naproxen plus omeprazole and similar to placebo. However, this study included healthy volunteers with short follow up of 16 days only. Another study compared the incidence of small bowel injury, as assessed by video capsule endoscopy, in 408 healthy subjects receiving celecoxib with those receiving ibuprofen plus omeprazole. Celecoxib was

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Table 1. Summary of Studies on the Different Interventions to Prevent NSAID-Induced Lower GI Injuries

Author (year)	Study design	Intervention	Study period	Subject	Main result
Selective COX-2 inhibitors					
Goldstein *et al.* (2007)[9]	Multicenter, double-blind RCT	Celecoxib (200 mg bid), ibuprofen (800 mg tid) plus omeprazole (20 mg qd) or placebo	2 wk	408 Healthy subjects	The mean number of small bowel mucosal breaks and the percentage of subjects with mucosal breaks were 0.7/25.9% for ibuprofen/omeprazole compared with 0.2/6.4% for celecoxib and 0.1/7.1% placebo (both comparisons p<0.001).
Hawkey *et al.* (2008)[10]	Double-blind RCT	Lumiracoxib (100 mg qd), naproxen (500 mg bid) plus omeprazole (20 mg qd), or placebo	16 day	139 Healthy volunteers	Acute small-bowel injury on lumiracoxib treatment is less frequent than with naproxen plus omeprazole and similar to placebo.
Laine *et al.* (2003)[11]	*Post hoc* analysis of a RCT	Naproxen (500 mg bid) or rofecoxib (50 mg qd)	9 mo	8,076 Patients with RA	The rate of serious lower GI events per 100 patient-years was 0.41 for rofecoxib and 0.89 for naproxen (RR, 0.46; 95% CI, 0.22–0.93; p=0.032).
Laine *et al.* (2008)[3]	Pooled data from 3 RCTs	Etoricoxib (60 or 90 mg qd) or diclofenac (150 mg qd)	18 mo	34,701 Patients with OA or RA	Lower GI clinical events rates were 0.32 and 0.38 per 100 patient-years for etoricoxib and diclofenac (HR, 0.84; 95% CI, 0.63–1.13).
Chan *et al.* (2010)[12]	Multicenter double-blind RCT	Celecoxib (200 mg bid) or diclofenac slow release (75 mg bid) plus omeprazole (20 mg qd)	6 mo	4,484 Patients with OA or RA	The rate primary endpoint during the 6-mo study period was 0.9% (95% CI, 0.5–1.3) in the celecoxib group and 3.8% (95% CI, 2.9–4.3) in the diclofenac plus omeprazole group (difference 2.9%, 95% CI, 2.0%–3.8%; p<0.0001).
Jarupongprapa *et al.* (2013)[13]	Meta-analysis of 9 RCTs	COX-2 inhibitors or NSAIDs plus PPI	2–24 mo	7,616 Patients with OA or RA, or healthy	COX-2 inhibitors were found to have significantly reduced the risk of major GI events, including perforation, obstruction, and bleeding (RR, 0.38; 95% CI, 0.25–0.56, p<0.001).
Misoprostol					
Bjarnason *et al.* (1989)[14]	RCT	Misoprostol (200 mg), indomethacin (75 mg), or coadministration	-	12 Healthy male volunteers	Indomethacin increased the permeation of ^{51}Cr-EDTA selectively, and this increase was significantly reduced by the coadministration of misoprostol.
Davies *et al.* (1993)[15]	Double-blind RCT	Metronidazole (400 mg bid) or misoprostol (200 μg qid), along with indomethacin (50 mg bid)	1 wk	16 Healthy volunteers	Metronidazole prevented ^{51}Cr-EDTA permeation increase (1.10 [0.39] before, 1.55 [0.54] after, p>0.05), whereas misoprostol did not (1.31 [0.51] before, 3.26 [1.10]) after, p=0.005).
Morris *et al.* (1994)[16]	Retrospective cohort study	Misoprostol (1,200 μg/day) or no treatment	-	21 Patients with NSAID-induced enteropathy	Haemoglobin in the misoprostol-treated group rose significantly from median (range) 9.1 (6.2–10.6) g/dL to 10.6 (6.5–16.8) g/dL (p=0.004).
Raskin *et al.* (1995)[17]	Multicdnter double-blind RCT	Placebo (qid); misoprostol (200 μg bid) and placebo (bid); misoprostol (200 μg tid) and placebo(qd); or micrograms (200 μg qid)	12 wk	1,197 Patients with upper GI symptoms during NSAID therapy	The incidence of duodenal ulcers was significantly lower in the groups receiving misoprostol bid (2.6%; difference, 4.9% [95% CI, 1.5%–8.2%]; p=0.004), tid (3.3%; difference, 4.2% [95% CI, 0.6%–7.7%]; p=0.019), and qid (1.4%; difference, 6.1% [95% CI, 2.6%–9.6%]; p= 0.007) compared with placebo.
Rostom *et al.* (2002)[18]	Meta-analysis of 40 RCTs	Misoprostol vs placebo, vs ranitidine, or vs PPI (23 RCTs on misoprostol)	-	-	Misoprostol 800 μg/day was superior to 400 μg/day for the prevention of endoscopic gastric ulcers (RR=0.17, RR=0.39 respectively, p=0.0055). Misoprostol caused diarrhea at all doses, although significantly more at 800 μg/day than 400 μg/day (p=0.0012).

Table 1. Continued

Author (year)	Study design	Intervention	Study period	Subject	Main result
Watanabe *et al.* (2008)[19]	Single arm study	Misoprostol (200 μg qid)	8 wk	11 Patients with aspirin-induced gastric ulcers	Misoprostol significantly decreased the median number of red spots and mucosal breaks.
Fujimori *et al.* (2009)[20]	Single-blind RCT	Diclofenac (25 mg tid) plus omeprazole (20 mg qd), or misoprostol (200 μg tid) plus diclofenac and omeprazole	2 wk	30 Healthy male volunteers	NSAID treatment significantly increased the mean number of mucosal breaks in the NSAID-PPI group (p=0.012). In contrast, there was no significant change before and after misoprostol cotreatment (p=0.42).
Kyaw *et al.* (2018)[21]	Multicdnter double-blind RCT	Misoprostol (200 μg qid) or placebo	8 wk	84 Aspirin users with small bowel bleeding	Complete healing of small bowel ulcers was observed in 12 patients in the misoprostol group (28.6%) and 4 patients in the placebo group (9.5%), for a difference in proportion of 19.0% (95% CI, 2.8%–35.3%; p=0.026).
Taha *et al.* (2018)[22]	Double-blind RCT	Misoprostol (200 μg qid) or placebo	8 wk	104 Aspirin or NSAIDs users with small bowel ulcers	Complete healing of small bowel ulcers and erosions was noted at week 8 in 27 (54%) of 50 patients in the misoprostol group and 9 of 52 patients (17%) in the placebo group (percentage difference, 36.7%; 95% CI, 19.5–53.9; p=0.0002).
COX-inhibiting nitric oxide donors					
Hawkey *et al.* (2003)[23]	Randomized crossover study	AZD3582 (a nitroxybutyl derivative of naproxen, 750 mg bid), naproxen (500 mg bid), or placebo	12 day	31 Healthy volunteers	The mean number of gastroduodenal erosions was 11.5 on naproxen vs 4.1 on AZD3582 (p<0.0001). Naproxen increased intestinal permeability whereas AZD3582 and placebo did not.
Fiorucci *et al.* (2004)[24]	RCT	NCX-4016 (800 mg bid), NCX-4016 (800 mg bid) plus aspirin (325 mg qd), aspirin, or placebo	21 day	48 Healthy subjects	NCX-4016 is equally effective as aspirin in inhibiting cyclooxygenase activity. However, NCX-4016 causes less gastric damage and prevents monocyte activation.
Lohmander *et al.* (2005)[25]	Double-blind RCT	AZD3582 (750 mg bid), naproxen (500 mg bid), or placebo	6 wk	970 Patients with OA	The incidence of ulcers with AZD3582 was 9.7% and with naproxen 13.7% (p=0.07, NS), vs 0% on placebo. Most secondary endoscopic GI end points favored AZD3582.
Intestinal microbiota modulation					
Bjarnason *et al.* (1992)[26]	Single arm study	Metronidazole 800 mg/day	2–12 wk	13 Patients using NSAIDs	Intestinal inflammation and blood loss were significantly reduced after treatment. There were no significant changes in intestinal permeability, or endoscopic or microscopic appearances of the gastroduodenal mucosa.
Montalto *et al.* (2010)[27]	Randomized crossover study	A daily dose of probiotic mixture (VSL#3) or placebo	21 day	20 Healthy volunteers	Treatment with VSL#3 before and during indomethacin therapy significantly reduces FCCs in healthy subjects with respect to placebo.
Endo *et al.* (2011)[28]	RCT	Probiotic with *Lactobacillus casei* for (*L. casei* group) or control group	3 mo	25 Aspirin users with unexplained iron deficiency anemia	Significant decreases in the number of mucosal breaks and the capsule endoscopy score were observed at the 3-mo evaluation in the *L. casei* group as compared with the results in the control group (p=0.039).

Table 1. Continued

Author (year)	Study design	Intervention	Study period	Subject	Main result
Mucoprotective agents					
Niwa *et al*. (2008)[29]	Randomized crossover study	Rebamipide or placebo along with dicloenac	6 wk	10 Healthy subjects	The number of subjects with small-intestinal mucosal injuries was higher in the placebo group (8/10) than in the rebamipide group (2/10) (p=0.023).
Thong-Ngam *et al*. (2009)[30]	Single arm study	Rebamipide (100 mg tid)	8 wk	30 Patients with gastric ulcer	Rebamipide is effective and well tolerated for treatment of gastric ulcers especially those caused by NSAIDs, as it promotes the improvement of gastric inflammation scores, clinical symptoms, and ulcer healing.
Fujimori *et al*. (2011)[31]	Double-blind RCT	Rebamipide (300 mg/day), or placebo along with diclofenac (75 mg/day) and omeprazole (20 mg/day)	14 day	72 Healthy male volunteers	NSAID therapy increased the mean number of mucosal injuries from 0.1 to 16 and 4.2 in the control and rebamipide groups, respectively, but not significant. For subjects with mucosal injuries, rebamipide tended to decrease mucosal injuries from 25 in the control to 8.9 in the rebamipide group (Mann-Whitney U test; p=0.038).
Mizukami *et al*. (2011)[32]	Randomized, crossover study	Rebamipide (300 mg/day) or placebo, along with aspirin (100 mg qd) and omeprazole (20 mg qd)	12 wk	11 Healthy male subjects	Rebamipide significantly prevented mucosal breaks on the ileum compared with the placebo group (p=0.017 at 1st wk and p=0.027 at 4th wk).
Mizukami *et al*. (2012)[33]	Randomized, crossover study	Rebamipide (300 mg/day) or placebo, along with aspirin (100 mg qd) and omeprazole (20 mg qd)	12 wk	12 Healthy male subjects	For the subjects receiving rebamipide, the total prevalence of lower GI symptoms was significantly different from the placebo group (p=0.0093) at wk 4.
Zhang *et al*. (2013)[34]	Meta-analysis of 15 RCTs	Rebamipide vs placebo, or vs PPI, or vs misoprostol, or vs H2RA	-	965 Subjects	Rebamipide acted better than placebo against NSAID-induced GI injury, which was equal to or not superior to traditional strategies (PPIs, H2RA, or misoprostol). Rebamipide showed a beneficial effect against the small bowel damage (RR, 2.70; 95% CI, 1.02–7.16; p=0.045) vs placebo.
Kurokawa *et al*. (2014)[35]	Multicenter, double-blind RCT	Rebamipide (100 mg tid) or placebo	4 wk	61 Patients with NSAIDs-induced enteropathy	Rebamipide has not only the healing effect for NSAIDs-induced enteropathy compared with placebo, but the improvement of nutritional condition.
Watanabe *et al*. (2015)[36]	Multicenter, double-blind RCT	Rebamipide (300 mg tid) or placebo	8 wk	38 Patients with aspirin-induced enteropathy	High-dose rebamipide is effective for the treatment of LDA-induced moderate-to-severe enteropathy.
Ota *et al*. (2016)[37]	RCT	Omeprazole 10 mg, rebamipide 300 mg, or rebamipide 900 mg, along with aspirin	2 wk	45 Healthy volunteers	The fecal calprotectin levels only increased significantly in group A. The gastroscopic and capsule endoscopic findings and the fecal occult blood test findings did not differ significantly among three groups.

Table 1. Continued

Author (year)	Study design	Intervention	Study period	Subject	Main result
Kuramoto *et al.* (2013)[38]	RCT	Group I: diclofenac (75 mg daily) and irsogladine (4 mg daily); or group O: diclofenac and omeprazole (10 mg daily)	14 day	32 Healthy volunteers	No significant difference between group I and O in the upper GI lesion score change. NSAID significantly increased the mean number of small intestinal mucosal breaks in group O (p=0.0002), not in group I. The between-group difference was significant (p=0.004).
Isomura *et al.* (2014)[39]	Single-blind RCT	Irsogladine (4 mg/day) or the control group	4 wk	41 Patients with NSAID-induced small intestinal injury	The improvement rate was significantly higher in the irsogladine group (16/19 patients; 84.2%) than in the control group (9/20 patients; 45.0%; p=0.02).
Kojima *et al.* (2015)[40]	RCT	Omeprazole (10 mg/day) for 6 wk, with irsogladine (4 mg/day) from 6 wk to 10, or irsogladine for 6 wk, or omeprazole for 10 wk, along with diclofenac (75 mg/day)	6 wk	37 Healthy volunteers	Irsogladine was effective in both preventing and healing such lesions.
Shim *et al.* (2018)[41]	Multicenter, double-blind RCT	Irsogladine maleate (2 mg bid) or placebo	8 wk	76 Patients using NSAIDs or aspirin	There were no significant differences in gastric protective effects between test and placebo groups. However, 2 cases of peptic ulcer in the placebo group but none in the test group were observed.
Other					
Hayllar *et al.* (1994)[42]	RCT	Sulfasalazine (1.5–3.0 mg/day) or another antirheumatic drug	6–12 mo	46 Patients with RA	Sulfasalazine reduced both intestinal inflammation and blood loss, whereas the other antirheumatic drugs did not.
Ota *et al.* (2019)[43]	Double-blind RCT	Group A, low-dose aspirin; group B, low-dose aspirin and 4.0 g of ecabet sodium	2 wk	24 Healthy volunteers	A significant difference was found in the median number of small intestinal lesions before or after treatment in group A (baseline: 1 [0–5], after: 5 [1–11]; p=0.0059) but not in group B (baseline: 0.5 [0–9], after: 3 [0–23]; p=0.0586).
Iguchi *et al.* (2018)[44]	RCT	Aspirin 100 mg/kg daily or aspirin plus egualen sodium 30 mg daily.	2 wk	20 Healthy male volunteers	Egualen sodium significantly suppressed the total number of small intestinal injuries detected by capsule endoscopy and the positive ratio for the fecal occult blood test.
Huang *et al.* (2014)[45]	RCT	Diclofenac (75 mg bid) plus omeprazole (20 mg/day), or muscovite (3 g bid) plus diclofenac and omeprazole	14 day	30 Healthy volunteers	A significant difference was observed in number of subjects with mucosal breaks comparing muscovite with the control. Co-administration of muscovite reduced the rate of mucosal break to 31.3% (5/16) (p=0.028).

NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal; RCT, randomized controlled trial; qd, one a day; bid, twice a day; tid, 3 times a day; qid, 4 times a day; RR, relative risk; CI, confidence interval; RA, rheumatoid arthritis; OA, osteoarthritis; HR, hazard ratio; PPI, proton pump inhibitor; EDTA, ethylenediamine tetraacetic acid; FCCs, faecal calprotectin concentrations; H2RA, histamine type-2 receptor antagonists; LDA, low-dose aspirin.

also associated with significantly fewer small bowel mucosal breaks than ibuprofen and omeprazole.[9] A larger RCT[11] involving 8,076 rheumatoid arthritis patients reported that rofecoxib reduced the serious lower GI side effects (bleeding, perforation, obstruction, ulceration, or diverticulitis) by 54% when compared to naproxen with the rate of 0.41 and 0.89 per 100 patient-years (RR, 0.46; 95% CI, 0.22 to 0.93), respectively. The CONDOR study[12] is another RCT involving 4,484 patients which found that celecoxib was associated with a lower risk of adverse events throughout the GI tract when compared with diclofenac plus omeprazole. However, in the MEDAL study in which 34,701 patients were included, there was no statistically significant difference between etoricoxib[3] and diclofenac in lower GI clinical events (perforation or obstruction requiring hospitalization or bleeding).

A systematic review of randomized trials, including nine trials with 7,616 participants, compared GI adverse effects between COX-2 inhibitors and NSAIDs plus proton pump inhibitor (PPI) and found that COX-2 inhibitors significantly reduced the risk of major GI complications, perforation, obstruction and bleeding (RR, 0.38; 95% CI, 0.25 to 0.56).[13] However, after stratifying into upper, mid or lower GI tract, it was not significant for upper (RR, 0.83; 95% CI, 0.36 to 1.89) and lower GI complications (RR, 0.29; 95% CI, 0.01 to 4.18). In contrast, significant difference was detected in mid GI complications (RR, 0.38; 95% CI, 0.16 to 0.89) which favored COX-2 inhibitors. Based on current evidences, some selective COX-2 inhibitors, such as celecoxib and rofecoxib, could be an alternative to traditional NSAIDs to prevent lower GI damage.

MISOPROSTOL

It is generally considered that prostaglandins are important in the mediation of inflammation and maintenance of mucosal integrity of the GI tract.[50] While inhibition of prostaglandin synthesis through COX is one of the major mechanisms of NSAIDs induced GI tract injury,[51] supplementation with misoprostol, a prostaglandin analog, may be effective in protecting against NSAIDs induced enteropathy.[50] Morris *et al*.[16] reported that high dose (1,200 μg) misoprostol therapy was associated with an improvement in anemia with an increase of hemoglobin in patients with proven NSAID enteropathy in a retrospective study of 21 patients. Bjarnason *et al*.[14,52] also found that co-administration of misoprostol with NSAIDs alleviated the indomethacin-induced increase in intestinal permeation. However, the study of Davies *et al*.[15] showed that the protective effects of misoprostol (800 μg) on the intestinal permeability co-administration with indomethacin was limited. It was suggested that prostaglandin alleviation of NSAID-induced intestinal permeability may be dose-dependent or that intestinal permeability may only be partially mediated by reduced mucosal prostaglandins.[53] This dose-response effect was also found in study comparing the efficacy of three misoprostol dosing regimens in the prevention of gastric and duodenal ulcers associated with long-term NSAIDs.[17,18]

The protective effects of misoprostol were further demonstrated in studies evaluating small intestine damage by capsule endoscopy. Watanabe *et al*.[19] reported that misoprostol (200 μg given 4 times daily) improved the mucosal lesions found in the small intestine by capsule endoscopy in a case series of 11 patients who had developed gastric ulcers induced by low-dose enteric-coated aspirin. A pilot RCTs by Fujimori *et al*.,[20] involving 34 healthy volunteers, showed that misoprostol (200 μg given 3 times daily) co-therapy reduced the incidence of small-intestinal mucosal breaks induced by a 2-week administration of diclofenac sodium. Recently, Kyaw *et al*.[21] performed an RCT of 84 aspirin users with small bowel bleeding who required aspirin therapy and found that misoprostol (200 μg given 4 times daily) for 8 weeks was superior to placebo in healing of small bowel ulcers. Similar results were also reported in another randomized trial by Taha *et al*.[22] Though the potential protective effects of misoprostol were observed in these studies, large clinical trials with long-term outcomes are lacking. Furthermore, significantly increased risk of drug-related adverse effects like abdominal pain, nausea or vomiting, diarrhea and high dropout rate related to the use of misoprostol were observed in clinical trials.[18,22]

COX-INHIBITING NITRIC OXIDE DONORS (CINODS)

It has been shown that nitric oxide (NO) plays a key role in the maintenance of the GI mucosa.[54,55] NO and prostaglandin showed similar gastroprotective actions that they are both capable of modulating mucosal blood flow, mucus release, and repair of mucosal injury.[56,57] Hence, cyclooxygenase inhibiting nitric oxide donators (CINODs) are a new class of anti-inflammatory and analgesic drugs, in which NO is coupled to an NSAID, could potentially minimize GI toxicity of traditional NSAIDs.[57,58]

In early animal studies, though prostaglandin was still suppressed, NO-releasing derivatives of a wide range of NSAIDs, including aspirin, flurbiprofen, naproxen, and diclofenac, have been shown to minimize the GI injury.[58-62] Different from conventional NSAIDs or selective COX-2 inhibitors, which exacerbate experimental colitis in rats[63] or inflammatory bowel disease in humans,[64] NO-releasing diclofenac was found to be well tolerated by rats with colitis.[65] Several clinical studies have also shown consistently that CINODs cause less upper GI damage.[23-25] However, there is no clinical studies that evaluate the effects of CINODs in the lower GI tract.

INTESTINAL MICROBIOTA MODULATION

Accumulating evidences suggest that intestinal bacteria may play a significant role in the pathogenesis of small-bowel dam-

age induced by NSAIDs and that enterobacterial translocation into the mucosa represents the first step of a series of events leading to gross lesion formation.[66,67] It has been reported that germ-free mice were resistant to NSAIDs related intestinal damage.[68,69] However, when germ-free mice were colonized with jejunal bacteria from PPI-treated rats, the severity of NSAID-induced intestinal injury increased.[70] Therefore, modulating intestinal microbiota could be a new strategy in the prevention of NSAID-induced intestinal damage.[67,71]

In keeping with this, several studies reported that antibiotics could attenuate NSAIDs induced enteropathy.[66] A resent animal study showed that rifaximin treatment significantly prevents indomethacin-induced intestinal damage following with a decrease in tissue inflammation, oxidative stress and digestive bleeding as well as reversal of NSAID-induced alterations in bacterial population.[72] Colucci *et al*.[73] examined the pathophysiology of NSAID-associated intestinal lesions in a rat model and found that rifaximin prevents diclofenac-induced enteropathy through both anti-bacterial and anti-inflammatory activities. Other antibiotics like metronidazole, tetracycline, kanamycin, neomycin plus bacitracin and streptomycin were also reported to reduce the risk of NSAID induced enteropathy.[26,74-76] In addition, rifaximin also demonstrated protective effect in patients receiving long-term PPIs treatment, which eradicated 87% to 91% of cases of small intestinal bacterial overgrowth.[77] Nevertheless, current evidences supporting the effects of antibiotics in preventing NSAID-induced enteropathy are still weak and most of them were from animal models. Even though antibiotics showed protective effects on NSAIDs/PPIs induced enteropathy, the long-term efficacy and safety has not been confirmed and further large long-term clinical studies are necessary.

Probiotics is another approach in modulating the composition of intestinal flora and has been used in treating several GI disorders like inflammatory bowel diseases,[78] irritable bowel syndrome,[79] infectious diarrhea and antibiotic-induced diarrhea.[80,81] It has been suggested that probiotics could also protect against NSAID-induced enteropathy by modulating the intestinal microbiota.[82] Kinouchi *et al*.[74] found that the metabolites of *Lactobacillus acidophilus* and *Bifidobacterium adolescentis* inhibited ileal ulcer formation by repressing unbalanced growth of the intestinal microflora and lipid peroxidation in rats. NSAID-induced small bowel injury in rats could be alleviated after restoring small intestinal *Actinobacteria* through administration of selected commensal bacteria during treatment with PPI and NSAIDs.[70] It was also confirmed in a double-blind, cross-over study of 20 healthy volunteers taking the probiotic mixture (VSL#3) or placebo for 21 days, and found that treatment with VSL#3 before and during indomethacin therapy significantly reduces the intestinal inflammation.[27] A pilot randomized trial of 35 patients who took low-dose enteric-coated aspirin for more than 3 months plus omeprazole, also found that co-administration of *Lactobacillus casei* could decrease the number of mucosal breaks under capsule endoscopy.[28] However, the quality of evidence on protective effects of probiotics on NSAID-induced enteropathy are still low and further clinical trials are needed.

ROLE OF PPIs

Gastroprotective agents, especially PPIs, are typically co-prescribed to protect the upper GI tract from NSAIDs induced mucosal injury, which was also recommended by guidelines.[83] By suppressing gastric acid secretion, PPIs are effective in decreasing the risk of NSAIDs induced upper GI mucosal damage and bleeding, presumably by raising the pH of the stomach.[84] However, lower GI bleeding could be not protected by PPIs,[2] and emerging evidences further indicate that PPI may increase the risk of NSAIDs induced small bowel damage and bleeding.[70,85,86] A similar exacerbation of NSAIDs induced small bowel damage was also observed in H2 receptor antagonists.[85] It was suggested that long term use of PPIs may exacerbate NSAIDs induced small bowel injury by altering intestinal microbiota (dysbiosis) following acid suppression,[7,70] which is supported by small intestinal bacterial overgrowth observed in patients with long-term use of PPIs.[77,87] A recent multicenter case-control study found that the use of PPIs remained an independent risk factors for mid GI bleeding (adjusted OR, 1.94; p=0.034) even after adjusting for propensity score.[88] Thus, the use of PPIs is considered to be an independent risk factor associated with NSAID-associated enteropathy and should be used cautiously.

MUCOPROTECTIVE AGENTS

1. Rebamipide

Rebamipide, an amino acid derivative of 2-(1H)-quinolinone, is a mucosal protective drug that has been clinically used for treating gastritis and peptic ulcers.[30,89] Studies have shown that rebamipide is effective to alleviate the NSAIDs induced injury of GI tract, and more recently, the small intestine.[34,85] Rebamipide promotes the production of endogenous prostaglandins and modulates the composition of small intestinal microbiota, which supports its efficacy on NSAID-induced small intestinal damage.[90-92]

Small RCTs of healthy subjects supported that rebamipide had the potential to reduce NSAID-induced small intestinal injury.[29,31-33,37] Kurokawa *et al*.[35] performed a multicenter study involving 61 patients who had received more than 3 months of low dose aspirin and/or NSAID to take rebamipide (100 mg 3 times daily for 4 weeks) or placebo and found that rebamipide had the protective effect for NSAIDs-induced enteropathy by reducing the number of small intestinal ulcers and erosions as evaluated by capsule endoscopy. Another small multicenter study by Watanabe *et al*.[36] also found that 8 weeks of high-dose rebamipide (300 mg 3 times daily) significantly decreased the number of mucosal breaks and improved intestinal dam-

age severity. However, Ota *et al*.[37] reported that standard-dose rebamipide (100 mg 3 times daily) was sufficient for preventing mucosal injury of the small intestine induced by low-dose aspirin, indicating that high-dose rebamipide (300 mg 3 times daily) may not be necessary. A systematic review and meta-analysis[34] including 15 RCTs and 965 individuals, provided consistent results that rebamipide is effective and safe for defending against NSAID-induced lower GI injuries. However, most studies are with small sample size and short-term follow-up.

2. Irsogladine

Irsogladine, a phosphodiesterase inhibitor, is currently used as one of the anti-ulcer or gastroprotective agents for the treatment of gastric ulcer and gastritis.[93] Irsogladine could also prevent NSAIDs or aspirin-induced peptic ulcer and gastritis.[41] Furthermore, it has been reported that, in animal research, irsogladine also possessed protective effects against NSAID-induced small intestinal lesions.[85,94] This protective effect was further confirmed in clinical studies. The study by Kuramoto *et al*.[38] involving 32 healthy volunteers, found that co-administration of irsogladine for 14 days protected against NSAID-induced mucosal injuries throughout the GI tract, from esophagus to small intestine, which was significantly better than omeprazole. The result was consistent in the study of Isomura *et al*.[39] that co-therapy of irsogladine for 4 weeks was effective for reducing NSAID-induced small-intestinal mucosal injury compared with control, in which 41 patients taking conventional NSAIDs for more than 4 weeks were enrolled. Irsogladine also presented treatment effects which significantly decreased the number of small intestinal lesions induced by NSAIDs.[40]

3. Other

Apart from the above agents, there are several other drugs such as sulphasalazine,[42] ecabet sodium,[43] egualen sodium,[44] curcumin,[95,96] and muscovite,[45] which were reported to have a preventive effect on NSAIDs-induced small intestine injury. However, data is very limited for these agents.

SUMMARY

So far, effective prevention and treatment of NSAID-associated lower GI injury are lacking. Though various agents including selective COX inhibitors, misoprostol, antibiotics and mucoprotective agents have been considered as candidates for NSAID-induced intestinal injury, they are not properly evaluated in clinical trials. High-quality well-designed randomized, placebo-controlled trials with long-term follow up are needed to verify the efficacy of potential agents in preventing NSAID-associated lower intestinal injury.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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