Prevention of Traditional NSAID-Induced Small Intestinal Injury: Recent Preliminary Studies Using Capsule Endoscopy

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Key Words

Small intestine • Non-steroidal anti-inflammatory drugs •
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Abstract

Capsule endoscopy and balloon endoscopy, advanced modalities that now allow for full investigation of the entire small intestine, have revealed that non-steroidal anti-inflammatory drugs (NSAIDs) can cause a variety of abnormalities in the small intestine. Traditional NSAIDs can induce small intestinal injuries in over 50% of patients. Several studies have shown that the preventive effect of proton pump inhibitors does not extend to the small intestine, suggesting that concomitant therapy may be required to prevent small intestinal side effects associated with traditional NSAIDs use. Recently, several randomized controlled trials used capsule endoscopy to evaluate the preventive effect of certain drugs on NSAID-induced small intestinal injuries. These studies show that misoprostol and rebamipide have a preventive effect for NSAID-induced small intestinal mucosal injuries. However, these studies included only a small series of healthy volunteers and tested short-term NSAID treatment. Therefore, further extensive studies are clearly required to ascertain the beneficial effect of these drugs.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide. They are widely used to help relieve musculoskeletal pain and inflammation, but can cause serious upper gastrointestinal side effects including dyspepsia, peptic ulceration, and hemorrhage [1, 2]. Until recently, most studies on NSAID-associated injury have focused on the upper gastrointestinal tract, since the stomach and duodenum are the sites generally associated with major morbidity and mortality in the clinical setting. However, epidemiological studies suggest that NSAIDs may also increase the risk for lower gastrointestinal adverse events [3, 4]. One recent prospective trial showed that serious lower gastrointestinal events in rheumatoid arthritis patients taking NSAIDs may account for 40% of all serious gastrointestinal events that develop in these patients [5]. In addition, capsule endoscopy and double-balloon endoscopy [6, 7], advanced modalities that now allow for full investigation of the entire small intestine, have revealed that NSAIDs can cause a variety of abnormalities in the small intestine such as ulcerations, perforation, bleeding and diaphragm-like stricture [3, 4, 8–10].

Prevalence of NSAID-Induced Small Intestinal Injury

Indium-111-labeled white blood scintigraphy detected small intestinal inflammation in more than 50% of chronic NSAID users, and fecal tests found signs of intestinal permeability and inflammation in 44% of this class of patients [11]. Morris et al. [8] showed ulcerations by sonde enteroscopy in 7 of 15 (47%) rheumatoid arthritis patients on NSAID medication. In a recent study, Maiden et al. [12] found new intestinal lesions by capsule endoscopy in 68% of healthy volunteers who took NSAIDs for 2 weeks. Goldstein et al. [13] reported that 55% of subjects developed small intestinal injuries after 2 weeks of naproxen medication, with a mean of 2.99 mucosal breaks per subject. In Japan, small intestinal mucosal breaks were detected by double-balloon endoscopy in 51% of the NSAID users and 5% of those not taking NSAIDs [10].

Key Process of NSAID-Induced Small Intestinal Injury

NSAIDs are known to increase intestinal permeability, the magnitude of which is quantitatively related to the potency of their ability to inhibit cyclooxygenase (COX)-1 [14]. The precise mechanism by which the inhibition of COX by NSAIDs translates into injury of the small intestine is poorly understood. Nevertheless, the first step leading to small intestinal mucosal injury is considered to be the topical toxicity of NSAIDs, which induces the uncoupling of mitochondrial oxidative phosphorylation in epithelial cells [15]. This topical action is followed by increased mucosal permeability and inflammation [16], which appears to be a prerequisite for NSAID-induced small intestinal injury and ulceration. However, it has been clearly shown that COX-1 inhibition is also required to convert topical toxicity into ulcerative damage. Somasundaram et al. [16] have shown that co-administration of aspirin, a COX-1 inhibitor that is mainly absorbed through the stomach and duodenum, and dinitrophenol, which increases intestinal permeability through the disruption of mitochondrial activity, induces intestinal ulceration similar to that induced by indomethacin. These data suggest that the inhibition of COX-1 is likely to be a key process in intestinal ulceration. Nevertheless, it is still far from clear exactly how COX-1 is involved in the key process of intestinal ulceration.

COX-2 Inhibitor or Proton Pump Inhibitor for Small Intestinal Injury

Capsule endoscopy studies have shown that even concomitant administration of proton pump inhibitors failed to prevent NSAID-induced small intestinal injury in healthy volunteers [12, 13]. As for the prevention of NSAID-induced small intestinal injury, several studies have already shown that celecoxib, a selective COX-2 inhibitor, effectively reduces both the number of mucosal breaks per subject and the percentage of subjects with at least 1 mucosal break [13, 17]. COX-2 inhibitors were initially introduced to provide symptomatic pain relief along with reduced gastrointestinal risk. However, in 2005, a joint hearing of the US Food and Drug Administration Arthritis Committee and the Drug Safety and Risk Management Committee found that the use of COX-2 inhibitors is associated with increased risk of cardiovascular events. These recent events have led many physicians to consider the use of traditional NSAIDs in combination with a proton pump inhibitor, a recommendation found in major treatment guidelines for patients with a history of gastrointestinal events or for those at high risk of developing complications [4]. Indeed, many physicians are again using traditional NSAIDs in combination with proton pump inhibitors as the preferred preventive method against NSAID-induced gastrointestinal injury [18, 19]. However, studies have shown that the preventive effect of proton pump inhibitors does not extend to the small intestine, suggesting that concomitant therapy may be required to prevent small intestinal side effects associated with NSAID use. The recent studies of prevention of traditional NSAID-induced small intestinal injuries are introduced below.

Effects of Various Drugs on NSAID-Induced Small Intestinal Injury

Prostaglandin (Misoprostol)

It has been suggested that NSAID-induced inhibition of COX-1, a key molecule that catalyzes prostaglandin (PG) production, is involved in the disruption of the protective mechanism in the gastric mucosa [18]. It is widely known that PG is effective in preventing NSAID-induced gastric mucosal injury [19–21]. As for NSAID-induced small intestinal injuries, a sequence of events, such as an increase in the permeability of epithelial cells due to the direct toxic effect of NSAIDs, bacterial translocation, and inflammation through cytokine activation in the small

intestinal mucosa, have been suggested to be key elements in the induction of small intestinal ulceration in addition to a lack of PG [15, 16, 22]. As for injury to the small intestine, PG has been shown to reverse NSAID-induced changes in intestinal permeability, a local intestinal event that is considered to play a pivotal role in inflammation and injury [23]. Furthermore, the co-administration of misoprostol, a PGE₁ analog, has been shown to attenuate the effect of NSAIDs on intestinal permeability in humans [23]. Therefore, we investigated the effect of misoprostol on small intestinal injury induced by traditional NSAID (diclofenac) in a single-blind, randomized controlled study [24].

Capsule Endoscopy Study

Thirty-four healthy male volunteers were screened by capsule endoscopy. All eligible subjects ($n = 32$) were randomly divided into an NSAID-control group ($n = 16$) and NSAID-PG group ($n = 16$). All eligible subjects were administered diclofenac (75 mg/day) and omeprazole (20 mg/day) for a period of 2 weeks, and the NSAID-PG group assigned to receive misoprostol (600 µg/day) in addition to the original treatment. In this study, we calculated mucosal breaks in the small intestine to be defined as lesions with slough surrounding erythema. Examples of typical mucosal breaks are shown in figure 1. A total of 15 NSAID-control subjects and 15 NSAID-PG subjects completed the treatment; the entire small intestine of each subject was evaluated by capsule endoscopy. In the NSAID-control group, 2 weeks of NSAID treatment induced 44 mucosal breaks in 8 subjects, resulting in a mean of 2.9 ± 6.3 mucosal breaks per subject. In the NSAID-PG group, PG treatment reduced the number of mucosal breaks to 10 in 2 subjects (mean 0.7 ± 2.3). Thus, at post-treatment capsule endoscopy, the mean number of mucosal breaks per subject was significantly higher in the NSAID-control group than in the NSAID-PG group ($p = 0.028$). The percentage of subjects with at least 1 mucosal break at post-treatment was also significantly higher in the NSAID-control group (53.3%) than in the NSAID-PG group (13.3%) ($p = 0.002$). Three subjects in the NSAID-PG group and 1 subject in the NSAID-control group complained of slight diarrhea at the beginning of treatment [24].

In the present study, misoprostol was effective in preventing the development of small intestinal mucosal breaks in healthy individuals receiving a 2-week regimen of diclofenac. The percentage of subjects that were found to have mucosal breaks at baseline endoscopy was 10% in the present study, compared to reports of 7–14% in other

studies, indicating that co-administration of misoprostol can reduce the development of mucosal breaks in patients on NSAID medication down to approximately basal levels [13, 17, 25]. Taking into consideration previous reports and our data, it is likely that misoprostol can prevent both upper and small intestinal injuries associated with the use of traditional NSAIDs. Moreover, Watanabe et al. [26] reported that misoprostol (800 µg/day) prevented low-dose enteric-coated aspirin (100 mg/day)-induced small intestinal injuries in 4 out of 7 patients. There is a possibility that misoprostol can prevent not only NSAID- but also aspirin-induced small intestinal injury.

Rebamipide

As previously mentioned, the authors have shown that co-administration of misoprostol reduced the incidence of small intestinal lesions induced by 2-week administration of diclofenac [24]. However, misoprostol can induce intolerable side effects as reported previously [27]. Rebamipide has been used across Asia for the treatment of gastric ulcers and gastric lesions such as erosions and edema caused by acute gastritis [27–29]. It has been well documented that rebamipide increases endogenous PG levels, scavenges free radicals, and suppresses inflammation in the gastric mucosa [11, 30, 31]. Through these actions, rebamipide has been also shown to be useful in preventing NSAID-induced gastrointestinal injuries in clinical studies and animal experiments. In a randomized controlled trial of rheumatoid arthritis and osteoarthritis patients carried out in East Asian countries, the effectiveness of rebamipide was shown to equal that of misoprostol in preventing the incidence ratio of gastroduodenal ulcers caused by 12 weeks of NSAID medication [31]. In an animal experiment, rebamipide has been shown to inhibit increases in iNOS activity induced by indomethacin, thereby reducing small intestinal injury caused by NSAIDs in rats [32]. From all these data, it is reasonable to speculate that to some extent, rebamipide might serve to reduce small intestinal damage in patients on NSAID medication.

Capsule Endoscopy Studies

A preliminary study recently conducted by Niwa et al. [33] has shown that rebamipide effectively reduced the incidence of NSAID-induced small intestinal injury. Their positive data were obtained in a double-blind, randomized, cross-over study where subjects were treated with diclofenac (75 mg/day) and omeprazole (20 mg) in the presence or absence of rebamipide (300 mg/day) for 7 days. The study shows that the number of subjects with

Fig. 1. Example of a typical mucosal break. Mucosal breaks were defined as lesions with slough surrounded by erythema.

Fig. 2. Example of a typical denuded area. Denuded areas were defined as reddened areas without villi.

Table 1. Randomized controlled trials using capsule endoscopy evaluated prevention therapy for traditional NSAID-induced small intestinal injuries

Reports	n	Drop-out	Study design	NSAID	Evaluated drug	Period	Evaluated injuries	Ratio of subjects with injuries		Evaluation
								control	treatment	
Fujimori et al. [24]	34	4	single-blind	diclofenac	misoprostol	14	mucosal break	53% (8/15)	13% (2/15)	effective
Niwa et al. [33]	10	0	double-blind, cross-over	diclofenac	rebamipide	7	mucosal break, bleeding, redness	80% (8/10)	20% (2/10)	effective
Fujimori et al. [34]	80	8	double-blind	diclofenac	rebamipide	14	mucosal break, denuded area	63% (24/38)	47% (16/34)	injuries decreased
Niwa et al. [36]	10	0	double-blind, cross-over	diclofenac	geranylgeranylacetone	7	mucosal break, bleeding, redness	40% (4/10)	10% (1/10)	no statistical difference ^a

^a Geranylgeranylacetone reduced diclofenac-induced gastric and small intestinal injuries in all.

small intestinal mucosal injuries was higher in the placebo group (8/10) than in the rebamipide group (2/10) ($p = 0.023$). However, the study is notably small in size, with only 10 subjects. Therefore, we conducted a larger sample size study to re-evaluate the effect of rebamipide on diclofenac-induced small intestinal injuries in healthy subjects, in a double-blind, randomized controlled trial.

Eighty healthy male volunteers were randomly divided into a placebo group ($n = 40$) and a rebamipide group ($n = 40$). After evaluation by baseline capsule endoscopy, all eligible subjects were administered diclofenac and omeprazole for a period of 2 weeks. The placebo group was assigned to remain on the original diclofenac and omeprazole therapy with a placebo capsule, while the rebamipide group was assigned to receive a capsule filled with rebamipide in addition to the original treatment.

These doses were the same as in the previous study [34]. A total of 38 control subjects and 34 rebamipide subjects completed the treatment and were evaluated by capsule endoscopy. NSAID therapy increased the mean number of mucosal injuries per subject, from a basal level of 0.1 ± 0.3 to 15.9 ± 71.6 and 4.2 ± 7.8 in the control and rebamipide co-treatment groups, respectively, the difference between the two groups was not significant. Mucosal injuries consisted of both mucosal breaks (fig. 1) and denuded areas (fig. 2) in this study. These lesions are not associated with each other [35]. The difference in the percentage of subjects with at least one mucosal injury at post-treatment was also not significant (control 63%, rebamipide 47%). However, when we limited our analysis to subjects with mucosal injuries, rebamipide co-treatment significantly reduced the mean number of mucosal inju-

ries per subject, from 25.1 ± 89.3 in the placebo group to 8.9 ± 9.4 in the rebamipide group ($p = 0.038$). We found that rebamipide reduced the intensity of injury in subjects apparently susceptible to NSAID-induced small intestinal injuries. These data were presented at Digestive Disease Week 2009 in Chicago [34].

Other Drugs

Niwa et al. [36] also reported that geranylgeranylacetone reduced diclofenac-induced gastric and small intestinal injuries in all from 9.5 ± 8.5 in the placebo group to 2.6 ± 3.2 in the geranylgeranylacetone group evaluated by capsule endoscopy ($p = 0.027$). Analysis was limited to small intestinal injuries; the difference between the two groups was not significant. The data were obtained in a double-blind, randomized, cross-over study where subjects were treated with diclofenac and omeprazole in the presence or absence of geranylgeranylacetone (300 mg/day) for 7 days. Geranylgeranylacetone is a gastric mucosal-protective agent that is widely used in Japan and other Asian countries for the treatment of gastritis and gastric ulcers [37, 38]. Table 1 shows these four randomized trials using capsule endoscopy. Marchbank et al. [39] reported that Pacific whiting fish hydrolysate prevented indomethacin-induced permeability increasing. The study did not employ capsule endoscopy. Fish hydrolysate is claimed to be beneficial for a variety of gastrointestinal conditions, and the study showed it to be capable

of stimulating proliferation and migration of HT29 cells in vitro [40]. Data were obtained in a double-blind, randomized, cross-over study where subjects were treated with indomethacin (50 mg/day) for 5 days in the presence or absence of fish hydrolysate starting 2 days prior to indomethacin.

Conclusion

Although these trials found that misoprostol, rebamipide and fish hydrolysate were effective agents against the development of NSAID-induced small intestinal injury, the inherent limitations of these studies preclude the drawing of any firm conclusions. Firstly, these studies included only a small number of healthy volunteers. Secondly, the short-term NSAIDs and treatment tested is not typical of the clinical setting, where long-term NSAID therapies are the norm. Therefore, further extensive studies are clearly required to ascertain the beneficial effect of these drugs.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of the article.

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