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EDITORIAL

Prevention and management of non-steroidal anti-inflammatory drugs-induced small intestinal injury

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Abstract

Non-steroidal anti-inflammatory drug (NSAID)-induced small bowel injury is a topic that deserves attention since the advent of capsule endoscopy and balloon enteroscopy. NSAID enteropathy is common and is mostly asymptomatic. However, massive bleeding, stricture, or perforation may occur. The pathogenesis of small intestine injury by NSAIDs is complex and different from that of the upper gastrointestinal tract. No drug has yet been developed that can completely prevent or treat NSAID enteropathy. Therefore, a long-term randomized study in chronic NSAID users is needed.

Key words: Non-steroidal anti-inflammatory drugs; Small intestinal injury; Prevention; Treatment

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly used pharmaceuticals worldwide. They are used for prevention and treatment of inflammatory diseases, arthritis, collagen diseases, pain, fever, and ischemic cerebrovascular disorders because of their anti-inflammatory, analgesic, antipyretic, and anti-platelet functions. In recent years, it has also been reported that they are effective for the prevention of colorectal cancer[1].

NSAIDs function by inhibiting cyclooxygenase (COX), the enzyme responsible for synthesis of prostaglandin. However, there are side effects with the use of NSAID-based therapy. The most common side effects are disorders of the digestive tract mucosa[2]. In addition to upper gastrointestinal complications, such as gastric and duodenal ulcers, complications in the small intestine and colon can occur, which cause bleeding, perforation, stricture, and chronic problems, such as iron deficiency anemia and protein loss[3].

The adverse effects of NSAIDs on the gastrointestinal tract are often unrelated to abdominal symptoms. In patients with suspected gastrointestinal bleeding, but who are not found to have bleeding lesions on gastroscopy and colonoscopy, NSAID-induced small intestine ulcerative lesions should be suspected[4]. The use of

NSAIDs has recently increased; therefore, increased awareness of the gastrointestinal side effects is needed. However, effective prevention and treatment of the side effects of NSAIDs in the small intestine have not yet been determined. In this manuscript, we review the studies conducted to date on the prevention and treatment of small intestine damage caused by NSAIDs.

EPIDEMIOLOGY

Until recently, gastrointestinal injury by NSAIDs was studied mainly in upper gastrointestinal organs, such as the stomach and duodenum, but there have been few studies on the small intestine. Among chronic NSAID users, up to 25% suffer from upper gastrointestinal ulcers, while bleeding or perforation occurs in 2%-4%[5].

Upper gastrointestinal complications in the stomach or duodenum are relatively easy to examine by endoscopy and upper gastrointestinal series, whereas it is more difficult to observe complications of the small intestine and determine the prevalence of injuries to this organ[6]. However, according to autopsy results published by Allison *et al*[2] in 1992, small intestinal ulcers were found in 0.6% of patients who did not take NSAIDs, whereas they were found in 8.4% of individuals taking NSAIDs. In more than 70% of arthritis patients receiving NSAID therapy for more than three months, intestinal inflammation accompanied by bleeding and protein loss was induced; even after the therapy ended, and these symptoms could persist longer than 16 mo[7]. Iron deficiency anemia due to blood loss in the small intestine was found in 41% of rheumatoid arthritis patients taking NSAIDs[1].

According to a recent study, gross damage was observed in 68% of volunteers who were administered 75 mg of diclofenac for 2 wk[8]. Another report found that macroscopic injury occurred in 80% of patients who took low doses of aspirin for 2 wk[9]. NSAID-related damage mainly occurred in the distal small bowel and colon, most commonly in the ileocecal region[10].

PATHOGENESIS

Administering NSAID increases intestinal permeability within 12 h and inflammation in the small intestine within 10 d[10]. The mechanism underlying small intestine injury by NSAIDs, unlike complications of the upper gastrointestinal tract, has not been elucidated because of the presence of intestinal bacteria in the small intestine and other complicating factors. The results of studies on the mechanism of injury by NSAIDs are still not sufficient, but can be summarized as combined systemic and local effects.

Currently, this has been described as a "three hit hypothesis"[3]. First, the phospholipids in cell surface membrane are damaged by direct injury by the NSAID, and damage to mitochondria within the cells subsequently occurs. Damage to mitochondria cause a reduction of energy generation within the cells (uncoupling of oxidative phosphorylation), release of intracellular calcium, and generation of free radicals. This leads to a decrease of integration between the cells and increased permeability of the small intestine. Through the increased intestinal permeability, various materials such as bile acids, food, intestinal bacteria, and proteolytic enzymes damage the weakened intestinal barrier and secondary inflammation occurs by the activation of neutrophils[3].

In experimental studies, Gram-negative bacteria invade the mucous membrane and activate Toll-like receptors, which are the receptors for Gram-negative bacterial lipopolysaccharide (LPS). It was reported that Toll-like receptors stimulate the inflammatory response and play an important role in small intestine damage[11,12].

If intestinal bacteria secrete endotoxins, intestinal bacterial translocation can occur. That is, LPS originating from endotoxins can spread to other places in addition to the intestine. LPS increases the expression of inducible nitric oxide synthase (iNOS) and iNOS leads to the production of peroxynitrite, the cytotoxic moiety from nitric oxide (NO) and superoxide. Ampicillin and metronidazole inactivate LPS and reduce iNOS expression[13].

Enterohepatic circulation plays an important role in gut injury. If NSAIDs do not enter the enterohepatic circulation, they will not damage the small intestine. For example, sundilac or aspirin, which do not enter the enterohepatic circulation, are less toxic to the small intestine[14]. However, if the intestine is continuously exposed to the drugs in the bloodstream *via* the enterohepatic circulation, damage may occur[14].

NSAIDs are conjugated to acryl glucuronides in the liver and excreted through the canalicular membrance of hepatocytes into bile[15]. Electrophilic NSAID-acyl glucuronides contact the brush border proteins of the enterocyte, causing the uptake of the NSAID into the cell. Acyl glucuronide also plays a role in the transport of NSAIDs to the target site-the distal part of jejunum/ileum. However, the role of acyl glucuronides in NSAID enteropathy is not yet clear.

There are two types of COX: COX-1 and COX-2. Prostaglandins derived from COX-1 are considered to be important for maintaining intestinal mucosa homeostasis. Previously, it was found that COX-1 had "housekeeping" characteristics, and inhibition of this factor reduced blood circulation in the mucosa and increased intestinal permeability, thereby causing injury to the gastrointestinal tract. Inhibition of COX-2 is not associated with gastrointestinal damage[16]. However, in a recently study using an animal model, intestinal mucosa damage occurred when both COX-1 and COX-2 were inhibited[17]. This finding suggests that COX-2 acts as immunomodulator and is involved in the healing process of inflammation. Thus, there could be an immunological mechanism whereby the inhibition of COX-2 causes gastrointestinal damage[3].

Heme oxygenase-1 (HO-1) is the rate-limiting en-

zyme in heme catabolism, and the upregulation of HO-1 produces anti-inflammatory or anti-oxidative effects. HO-1 is thought to be involved in the inhibition of small intestinal damage associated with NSAID. Pretreatment with an HO-1 inhibitor, SnPP (tin-protoporphyrin Ⅸ), exacerbates damage to the small intestine by indomethacin. Lansoprazole ameliorates small intestine ulcers induced by indomethacin through the upregulation of HO-1[18].

DIAGNOSIS

In the past, the documentation of NSAID-induced enteropathy was based on the measurement of small intestine permeability and an analysis of indicators of inflammation, such as fecal calprotectin. In recent years, intestinal mucosa have been able to be viewed directly by capsule endoscopy and enteroscopy[19,20].

For diagnosis, there should be a history of NSAID use, no history of antimicrobial agent use, and no bacterial growth in the stool or tissue cultures. There should be no vasculitis or granuloma in tissue specimens, and, after stopping an NSAID, clinical symptoms and the lesions found by endoscopy should disappear.

Intestinal permeability test

The intestinal permeability test, which examines damage to the intestinal barrier, is primarily used to measure the amount of an orally administered test reagent that is discharged in the urine[21]. Within 12 h after NSAID therapy, increased intestinal permeability can be observed. The material that is used for an intestinal permeability test is rarely absorbed into the normal intestinal barrier, but its absorption increases in damaged intestinal barrier, after which it is transported into the bloodstream and excreted in urine. Most of the material used for this test is excreted in urine within a certain time and is not metabolized *in vivo*[1]. The probes used in intestinal permeability tests include polyethylene glycol, cellobiose, sugars (such as lactulose and mannitol), and radionuclides, such as chromium-51-labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA). Of these, ^{51}Cr-EDTA is the most widely-used for measuring the damage by NSAIDs. It is not degraded by intestinal bacteria, reflects some of the colon permeability, and is used in a relatively simple assay. Increased intestinal permeability is observed in about 50%-70% of long-term NSAID users. Although the clinical usefulness of the intestinal permeability test is low, it has been used in a clinical study that observed the effects of food or drugs on the inhibition of intestinal damage caused by NSAIDs[1,6].

Measurement of intestinal inflammation

Intestinal inflammation by NSAIDs can be measured by scintigraphy using ^{111}Indium-labeled neutrophils[21]. In 50%-70% of individual taking NSAIDs for more than six months, labeled white cells were found to accumulate in the terminal ileum 20 h after administration, and a slight increase of inflammation was observed compared to patients with inflammatory bowel disease (IBD). This can be measured up to 16 mo after the patient has stopped taking the drug. However, this method is very expensive and it is difficult to apply in clinical tests. The detection of calprotectin in feces is used for detecting intestinal inflammation caused by NSAIDs, and inflammation is found in 44%-70% of long-term NSAID users. Excretion of ^{111}Indium in the stool is proportional to fecal calprotectin. However, it is also increased in individuals with IBD and colon cancer, unlike the intestinal permeability test, and has the disadvantage of low specificity for NSAID enteropathy[3,6].

Endoscopy

The recently introduced wireless capsule endoscopy and double-balloon enteroscopy can diagnose lesions, such as inflammation, erosions, and ulcers and complications including bleeding and stenosis, which are caused by NSAIDs[20]. In particular, capsule endoscopy, which is a non-invasive examination, is very useful. It can diagnose small bowel lesions in 70% of NSAID users and shows a high correlation with the fecal calprotectin test in measuring intestinal inflammation. Erosions or ulcers, which are the endoscopic findings of NSAID-induced enteropathy, can be caused by many factors besides NSAIDs, and histological examination cannot determine the cause of these lesions. Diseases for differential diagnosis include infection, IBD, ischemia, radiation enteritis, vasculitides, and drugs such as potassium chloride (KCl). The history of NSAID use, biopsy, and improvement of clinical symptoms after stopping the drug use are required for diagnosis. A diaphragm-like stricture is a characteristic finding, which is a secondary scar reaction of ulcer injury, and has non-inflammatory mucosa. There are usually multiple strictures occurring in the mid-intestine, ileum, and colon[22]. Maiden *et al*[19] classified the findings of capsule endoscopy into five groups: reddened folds, the denuded area, red spots, mucosal breaks, and blood. Graham[7] divided capsule endoscopy findings into red spots, small erosions, large erosions, and ulcers. In contrast, double-balloon enteroscopy has the advantages of directly treating bleeding lesions and the ability to perform histological examinations; however, it is a time-consuming and an invasive test[23]. Unfortunately, both tests incur relatively high costs, so their use is limited.

CLINICAL MANIFESTATION

In 60%-70% of NSAID-induced enteropathy, it is subclinical. This disorder displays nonspecific symptoms, such as iron deficiency anemia, gastrointestinal bleeding, hypoalbuminemia, vitamin B12 or bile acid malabsorption, diarrhea, and acute abdominal pain. Complications such as massive bleeding, stricture, and perforation may occur. These complications are rare, but can be fatal[6].

Gastrointestinal bleeding

Small intestinal injury caused by NSAIDs, even when not severe, can cause persistent bleeding and iron deficiency anemia. In patients with NSAID enteropathy, the sites of inflammation and bleeding are identical when measured by scintigraphy using ^{111}Indium-labeled neutrophils to observe intestinal inflammation, and technetium-99 m labeled red blood cell scintigraphy to show bleeding. In patients taking NSAIDs for rheumatoid arthritis who had severe anemia but no bleeding lesions observed by gastroscopy and colonoscopy, small intestinal ulcers have been observed in 47% when enteroscopy was performed. Generally, there is 2-10 mL of daily blood loss[4,6,24]. Apparent acute gastrointestinal bleeding is relatively rare and is caused by ulcers and erosions.

Protein loss

Protein loss in inflamed intestinal mucosa caused by the prolonged use of NSAID leads to hypoalbuminemia[1,3,6,24,25]. Previously, the loss of protein was thought to be secondary to bleeding, but it may occur without anemia. A gross bleeding lesion may not be found in the intestine of patients with enteropathy accompanied by loss of protein[24]. Nowadays, it is thought that protein loss associated with enteropathy can occur without lesions, such as inflammation, erosions, or ulcers.

Perforation and obstruction

Perforation associated with NSAID use is an uncommon complication that has a risk similar to that of bleeding. A case of perforation in a patient treated with high doses of indomethacin was reported[6,24].

Chronic ulcers caused by NSAID result in fibrosis and diaphragm-like strictures. Multiple diaphragm-like septa of 1-4 mm-thickness form in the middle part of the small intestine. If the intestinal lumen is narrowed, obstruction of the small intestine occurs in 17% of patients with NSAID-induced small intestinal ulcers[6]. This is associated with the drug dosage and duration, and accompanied by diarrhea, weight loss, iron deficiency anemia, and protein loss[24].

PREVENTION AND TREATMENT

There is still no proven method of preventing or curing small intestine damage due to NSAIDs. The simplest method is to stop taking the drugs. NSAIDs in prodrug and enteric-coated forms, and ones with controlled release have been developed, but they do not inhibit damage to the small intestine. In addition, H2-blocking agents and sucralfate that have effects on upper gastrointestinal complications are not useful for treating or preventing NSAID-related small intestinal damage, and the effect of proton pump inhibitors (PPI) has not yet been proven[26].

COX-2 selective inhibitor

The development of COX-2 selective inhibitors was expected to significantly reduce gastrointestinal complications caused by NSAIDs. COX-2 selective inhibitor reduced NSAID-associated upper gastrointestinal complications, but the effect on complications of the small intestine has yet to be proven. Currently, short-term treatment with COX-2 selective inhibitors has shown no effect on small intestinal permeability[27]. There have been some reports that symptoms of enteropathy are not observed in patients treated for short periods of time with COX-2 selective inhibitors[27-30]. However, it was also reported that the symptoms of patients treated with COX-2 inhibitors for more than three months were no different to those of patients treated with traditional NSAIDs[31,32]. An underlying reason for this observation is that selective COX-2 inhibitors also have some inhibitory effects on COX-1, and COX-2 has a role in the regulation of mucosal blood flow in some tissues. In addition, COX-2 inhibition increases leukocyte adherence without changes in the bloodstream. COX-2 may have an anti-inflammatory role in the vasculature, and COX-2 selective inhibitor has the disadvantage of adverse cardiovascular side effects.

NO, hydrogen sulfide-releasing NSAID, and zinc-NSAID

It has been reported that COX inhibiting NO donator, hydrogen sulfide-releasing NSAID, and zinc-NSAID prevent NSAID-induced gastrointestinal damage by vasodilation, anti-inflammation, and some cytoprotective actions[33]. Exogenous NO plays a role in maintaining mucosal integrity in the gastrointestinal tract by modulating mucosal blood flow and mucus secretion. Combining an NO donor drug with naproxen or aspirin provides protection from damage by NSAID[34]. Hydrogen sulfide has vasodilation, anti-oxidant, and anti-inflammatory effects[35,36].

Metronidazole

Metronidazole is an antibiotics used to treat anaerobic pathogen infections. When administered (800 mg/d), this drug decreases intestinal inflammation and blood loss caused by NSAID, but does not affect intestinal permeability[37]. Microbes sensitive to metronidazole are major neutrophil chemoattractants in NSAID enteropathy. However, other antibiotics except metronidazole are not effective for treating small intestinal damage caused by NSAIDs. The impact of metronidazole is not achieved by the effect on intestinal bacteria but by the inhibition of oxidative phosphorylation in the mitochondria of the intestinal cells[3].

Sulfasalazine

Sulfasalazine reduces NSAID-induced inflammation and blood loss[38]. The beneficial effect of sulfasalazine on rheumatoid arthritis seems to be due to the sulphapyridine moiety not to its 5-aminosalicylic acid moiety[39]. However, its role is unclear in NSAID-related enteropathy. It is useful in the ileitis of ankylosing spondylitis or for treating long-term NSAID users with rheumatoid

arthritis[38,39]. However, additional research is needed.

Rebamipide

Rebamipide increases mucus and stimulates the production of prostaglandin[40]. It also has anti-inflammatory properties. Rebamipide is a free radical scavenger and produces its effects by inhibiting superoxide production and suppressing myeloperoxidase activity[41]. Therefore, rebamipide can be expected to have an effect on intestinal inflammation. In a recent study, rebamipide prevented diclofenac-induced small bowel injury compared to a placebo[42].

Lansoprazole

Lansoprazole prevents the indomethacin-induced small bowel injury by upregulating HO-1, which has anti-inflammatory and anti-oxidative effects. This compound shows a broader PPI role in addition to its acid production suppression[18].

Goldstein *et al*[30] divided healthy volunteers into the three groups: a celecoxib group, a naproxen plus omeprazole group, and control group, and performed capsule endoscopy. Small bowel lesions were found in 16%, 55% and 7% of the individuals in each group, respectively. This indicates that small bowel lesions cannot be prevented with omeprazole. In other words, in the sites unaffected by gastric acid secretion, such as the small intestine, the increased mucosal protective effect of lansoprazole is more important.

Misoprostol

Misoprostol is a synthetic prostaglandin (PGE1) analog. It has a mucosal protective effect and effectively suppresses NSAID gastrointestinal side effects[43]. However, there is conflicting evidence for its effect on small bowel complications. In one report, misoprostol inhibited NSAID-associated intestinal permeability changes and showed a significant effect on enteropathy[44,45]. It was also found to be effective for treating enteropathy induced by low doses of aspirin[12]. However, misoprostol showed no significant effect on intestinal permeability in patients administered indomethacin in randomized controlled trials[46]. In this study, however, low doses of misoprostol were given for only one week, so additional research to verify these results is required. Misoprostol also has common side effects such as diarrhea, abdominal pain, headache, and constipation[3,6].

Eupatilin

Song *et al*[47] reported that eupatilin protects cultured feline ileal smooth muscle cells against cell damage caused by indomethacin. These protective functions are apparently due to eupatilin-mediated HO-1 induction through extracellular signal-regulated kinase and NF-E2-related factor-2 signal. Therefore, eupatilin is expected to lower the risk of complications such as ulcers, bleeding, and obstruction through its mucosal protective actions in chronic NASID users, but more systematic research is necessary.

Nutritional intervention

A period of time is needed for the prophylactic use of a drug; therefore, it would be better to use foods such as pharmaconutrients, which have relatively low pharmacological risks compared with drugs that have many side effects. Recombinant human lactoferrin has bactericidal, anti-inflammatory, and antioxidant activities, and can be taken orally as a supplement[48]. Commercial fish protein hydrolysate is a fermented fish product that is beneficial for the intestine[49]. Both recombinant human lactoferrin and fish hydrolysate reduce NSAID-associated intestinal permeability compared to a placebo.

Glutamine is a non-essential amino acid and used as energy sources of intestinal mucosa cells. It has been reported that after short-term administration of NSAIDs, glutamine is effective for the prevention of increased intestinal mucosa permeability[50]. In bovine colostrum, there are plenty of growth factors, such as insulin-like growth factor, various immunoglobulins, and antimicrobial peptides. Administration of bovine colostrum with glutamine is effective in reducing gut injury and transbacterial location caused by short-term administration of NSAIDs[51-53].

Other drugs

It was reported that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor fluvastatin has antioxidative activity and suppresses the formation of ileal ulcers caused by NSAIDs in rats[54]. Other HMG-CoA reductase inhibitors, pravastatin and atrovastatin, did not show these effects[54]. In addition, it was reported that the immunosuppressive drug tacrolimus (FK506) prevents small bowel ulcers caused by indomethacin in rats. This may be due to inhibition of iNOS induction by tacrolimus[55].

CONCLUSION

As capsule endoscopy and enteroscopy have recently become more widely used, NSAID-induced small intestinal damage has emerged as a clinically important issue. To reduce the risk of complications, such as ulcers, bleeding, and obstruction, in chronic NASID users, many researches have attempted to treat and prevent these disorders. To this end, metronidazole, sulfasalazine, COX-2 inhibitors, misoprostol, rebamipide, human lactoferrin, and fish protein hydrolate, have been examined, but there are currently no results of long-term administration. Thus, methods to effectively treat and prevent small bowel injury caused by NSAIDs are still lacking. Therefore, a long-term randomized study in chronic NSAID users is needed. In addition, careful monitoring and special attention for the indications of NSAIDs are required to avoid this disorder in individuals taking NSAIDs.

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