Current Prevention and Management of Non-steroid Anti Inflammatory Drugs Associated Gastroenteropathy

Fransiscus Ari, Dadang Makmun***

*Department of Internal Medicine, Faculty of Medicine, University of Indonesia
Dr. Cipto Mangunkusumo General National Hospital, Jakarta
**Division of Gastroenterology, Department of Internal Medicine
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

ABSTRACT

Non-steroid anti-inflammatory drugs (NSAIDs) are the most frequently used drugs to treat inflammation and are used almost in the whole world. However, NSAID is one of the important causes of gastroenteropathy development. NSAIDs enteropathy is frequently undetected because most of them are asymptomatic and required sophisticated examinations to diagnose. Not only non-selective cyclo-oxygenases (COX) inhibitor that can cause NSAID gastropathy, but selective COX-2 inhibitors may also cause gastrointestinal complications. NSAID gastroenteropathy require further evaluation and it may differ between patients.

Currently, there is no effective treatment available to treat gastrointestinal damage associated with NSAIDs administration. Identification of protective factors in gastrointestinal complication due to NSAIDs use is still a serious challenge. In this review, we will discuss the effect of NSAID administration towards gastrointestinal system, also the prevention and management strategies.

Keywords: *non-steroid anti-inflammatory drugs, gastroenteropathy, COX inhibitor, prevention, treatment*

ABSTRAK

Obat anti inflamasi non steroid (OAINS) adalah obat yang paling sering digunakan untuk terapi inflamasi dan digunakan hampir di seluruh dunia. Namun, OAINS merupakan salah satu penyebab penting terjadinya gastroenteropati. Enteropati OAINS seringkali tidak terdeteksi karena sebagian besar asimtomatik dan membutuhkan pemeriksaan yang canggih untuk mendiagnosisnya. Tidak hanya penghambat cyclo-oxygenases (COX) non-selektif yang menjadi penyebab gastropati OAINS, melainkan inhibitor COX-2 selektif dapat menimbulkan komplikasi gastrointestinal. Gastroenteropati OAINS membutuhkan pengkajian lebih lanjut dan berbeda antar pasien.

Sampai saat ini belum ada terapi yang efektif untuk kerusakan gastrointestinal terkait penggunaan OAINS. Identifikasi dari faktor-faktor protektif pada komplikasi gastrointestinal akibat penggunaan OAINS masih merupakan tantangan yang serius. Dalam makalah ini dibahas mengenai efek penggunaan OAINS terhadap sistem gastrointestinal serta strategi pencegahan dan tatalaksananya.

Kata kunci: *obat anti inflamasi non steroid, gastroenteropati, penghambat COX, pencegahan, tatalaksana*

INTRODUCTION

Non-steroid anti-inflammatory drugs (NSAIDs) is the most frequently prescribed drug group in the world.[1] The main population target which often receive this therapy is elderly with higher morbidity and mortality towards the occurrence of drug toxicity effect.[2] NSAIDs are used widely to treat clinical symptoms in inflammatory condition and also to overcome pain.

Additionally, low dose aspirin (acetylsalicylate acid or ASA) is used for primary and secondary prevention of cerebrovascular and cardiovascular diseases.[3] This group of drugs inhibit prostaglandin biosynthesis to produce therapeutic effects.[4]

Main adverse effects in NSAIDs administration include disturbance in the gastrointestinal, nervous system, kidney, and allergy. NSAIDs toxicity towards gastrointestinal has been widely known, particularly in gastroduodenal region.[2] Gastrointestinal disturbances which happen vary from dyspepsia complaints to gastroduodenal ulcer and bleeding.[1] NSAIDs gastropathy (aspirin) is initially found by Douthwaite and Lintott in 1938 through endoscopy findings.[5] A meta-analysis study showed, based on endoscopy examination, approximately one third patients who received long term NSAID had gastric or duodenal ulcer.[6]

Based on data from Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), there were 1.3% patients who were treated with NSAID were hospitalized due to severe gastrointestinal complications in USA and Canada population, with 1 year mortality rate ranges between 0.11-0.22%.[7] Based on other reports, gastric erosion is found in 50% patients consuming NSAIDs, with 2-4% from this group suffered from significant gastrointestinal ulcer and bleeding.[8] Meanwhile, in a patient autopsy data based study, patients who use long term NSAIDs had the incidence of small intestinal ulcer of 8% as compared to 0.6% in patients who had no history of NSAIDs administration.[9] Enteropathy due to the use of NSAIDs received less attention because they usually caused no symptoms and are not easy to detect.[10]

NSAIDS GASTROENTEROPATHY: PHYSIOLOGY ASPECT

Non steroid anti-inflammatory drugs (NSAIDs) can be classified into several groups based on the chemical structure and mechanism of action (Table 1). This drug decreases pain and inflammation through the blocking of *cyclo-oxygenases* (COX), enzyme required for prostaglandin production. Most NSAIDs inhibit two *cyclo-oxygenases*, which are COX-1 and COX-2.[3] COX-2 enzymes are mostly found in joints and muscles and contribute to the appearance of pain and inflammation. NSAIDs may cause bleeding due to the effect of these drugs in inhibiting COX-1 enzyme that is important in mucosal protection towards gastric acid. Morbidity and mortality rate due to gastrointestinal complication in the use of NSAIDs increase along with the increase of age (Table 2).[11] Besides age, there are other several risk factors which have high risk in the occurrence of gastrointestinal complications, including previous peptic ulcer history, *Helicobacter pylori (H. pylori)* infection, in the first month of NSAIDs administration, high dose NSAID usage, and other comorbid conditions (particularly cardiovascular), and the use of anticoagulants and corticosteroid.[1]

Table 2. Risk of gastrointestinal bleeding in 1 year administration of NSAIDs[11]

Age group (Years old)	Bleeding risk (Risk in 1 year is 1 in:)	Mortality rate due to bleeding
16-45	2100	12353
45-64	646	3800
65-74	570	3353
>75	110	647

Table 1. NSAIDs classification[4]

Types	Chemical components	General name of drugs
Salicylates	Second generation - *hydroxybenzoic acid* (*salicylic acid*)	Aspirin, diflunisal, and salsalate
Proprionate acid "profens" derivatives	Derivatives of *arylacetic acids*	Ibuprofen, dexibuprofen, ketoprofen, dexketoprofen, naproxen, fenoprofen, flurbiprofen, oxaprozin, and loxoprofen
Acetic acid derivatives	Acetic acid derivatives	Indomethacin, diclofenac, nabumetone, tolmetin, sulindac, etodolac, and ketorolac
Derivatives of *Enolic acid* "oxicams"	Fourth generation-*hydroxy benzothiazine Heterocycle*	Piroxicam, isoxicam, meloxicam, tenoxicam, droxicam, and lornoxicam
Derivatives of *Fenamic acid* "fenamates"	Derivatives of *anthranilic acid*	Mefenamic acid, flufenamic acid, tolfenamic acid, and meclofenamic acid
Phenylpyrazolones	First generation-*aryl-3,5-Pyrazolidinedione*	Phenylbutazone, oxyphenbutazone
Selective COX-2 inhibitor	*Diaryl-5-membered heterocycles*	Celecoxib, rofecoxib, and valdecoxib
Anilides and Sulphoanilides	*Acetamides* from *aniline* with or without *4-hydroxy* or *4-alkoxy*	Acetaminophen, phenacetin, and nimesulide

NSAIDs, including aspirin, cause damage to the gastric mucosa through two mechanisms, which are: systemic inhibition of endogenous prostaglandin synthesis in the mucosa and direct irritation or topical effect to the gastric epithelium. Inhibition of endogenous prostaglandin synthesis in the mucosa is caused by inhibition of COX enzyme, which converts arachidonic acid into prostaglandin.[12] This adverse effect occurs due to the non-selective feature of NSAIDs and inhibition of COX-1 enzyme, where the anti-inflammatory role of this drug is through COX-2 enzyme inhibition. Currently, the use of selective COX-2 (such as celecoxib) has been reported to have weaker gastrointestinal effect. However, the use of selective COX-2 inhibitor also causes gastrointestinal complication. Hypothesis which explain this is that COX-2 also plays role in defence mechanism and recovery process of damaged mucosa.[13]

NSAIDs also have direct cytotoxic effect to the gastric mucosa. Several studies showed that this cytotoxic effect is not associated with inhibition activity of COX enzyme. Topical effect found in NSAIDs has acid characteristic (for example, aspirin), which cause accumulation of the ionized non-steroidal anti-inflammatory drugs (NSAID), also known as "ion trapping" phenomenon and decrease hydrophobicity of mucosal gel layer in gastric mucosa. This leads to increase membrane permeability and result in damage of the gastric mucosa. NSAIDs may also induce necrosis and apoptosis of the gastric mucosal cells. Administration of other preparation of NSAIDs, such as prodrugs, parenteral preparation, rectal, and enteric-coated may decrease damage to the mucosa due to topical effect. However, this group of drugs can still cause gastrointestinal complication through inhibition effect of endogenous protective prostaglandin.[4]

In addition to these two mechanisms, the use of NSAID is also followed by leukocyte adhesion (particularly neutrophil) to the vascular endothelium in gastrointestinal microcirculation. This play important role in the development of gastric ulcer.[13] Mechanism of gastropathy development due to neutrophil adhesion is a result of mechanical obstruction of the capillary flow and the formation of protease and free radicals during neutrophil activation.[3] Free radicals which formed will react with polyunsaturated fatty acids in the mucosa and cause lipid peroxidation and tissue damage. Other resources add one more mechanism, which is through the production of additional proinflammatory mediators. The inhibition of prostaglandin production by NSAIDs activates lipoxygenase pathway and increase leukotriene production. Leukotriene may stimulate inflammation and tissue ischemia, which cause the occurrence of gastric mucosal damage. Furthermore, other inflammatory mediators, including tumour necrosis factors are also increased.

Damage to the small intestinal mucosa (enteropathy) even until the bowel (colopathy) have different pathophysiology to the damage of gastroduodenal mucosa.[14,15] The incidence of enteropathy have more complex pathophysiology and may proceed in much longer time compared to NSAIDs gastropathy. Decrease of prostaglandin synthesis due to NSAIDs use resulted in fragile small intestinal mucosa towards damage and the process of mucosal recovery also decreases. However, different from what happened in NSAIDs gastropathy, in enteropathy the suppression of COX enzymes is not the main reason. Prostaglandin in the intestinal mucosa can be suppressed but the ulcer or bleeding does not appear. The increase of mucosal permeability is caused by topical NSAIDs irritation effect. The essential pathophysiology in ulcer formation in the intestine is the presence of NSAIDs reabsorption in ileum and through enterohepatic circulation, again secreted in the duodenum. Bile duct ligation is said to prevent the happening of NSAIDs enteropathy by inhibiting enterohepatic circulation. Damage due to NSAIDs in the intestinal mucosa may also progress if they are combined with bile acid. Oxidative phosphorylation reaction is suspected to be the main mechanism in the occurrence of epithelial layer damage.[14] Leukocyte adhesion in the vascular endothelia has an important role in the occurrence of NSAIDs gastropathy, is not proved to happen in NSAIDs enteropathy. Although neutrophil infiltration may play role in the tissue damage if ulceration has occurred. There was evidence of *tumour necrosis factor-alpha* (TNF-α) involvement in NSAIDs enteropathy, but not directly associated with leukocyte adhesion in vascular endothels.[14]

Clinical Manifestation and Diagnostic Aspect of NSAIDs Gastroenteropathy

Clinical manifestation of NSAIDs gastropathy varies on the severity degree from the occurring erosion or ulcer. Upper digestive tract bleeding, perforation, and obstruction are the most serious and life-threatening clinical symptoms. Depending on the bleeding site, it may be in the form of occult bleeding, melena, or hematemesis. Clinical symptoms of NSAIDs gastropathy can be seen in Table 3.[3]

Table 3. Clinical manifestations of NSAIDs gastropathy[3]

General complaints	Epigastric pain, or may be accompanied by severe upper gastrointestinal complications.
Signs	Loss of body weight with nausea, vomitus, and anorexia. Complications may be in the form of bleeding, perforation, or obstruction
Symptoms	Abdominal pain Nocturnal pain (midnight up to 3 am) which awakened patient from sleep. *Heartburn*, burping, and bloating that accompanied abdominal pain. Nausea, vomitus, and anorexia (often associated with gastric ulcer) Symptoms may present seasonal, worsened in spring or autumn. Appear in episodes in several weeks and may experience remission in several weeks or months, even years

Clinical manifestations of NSAIDs are more vary, unspecific, and usually asymptomatic, although serious clinical symptoms, including bleeding, ileus, and perforation may also happen and be life-threatening. The most frequent clinical symptoms are occult gastrointestinal bleeding. Bleeding is associated with inflammation process and ranges for 2-10 mL per day.[12] Obvious and acute bleeding rarely happen. This may occur in erosion and ulceration. In patients with NSAIDs enteropathy, there were only 5-10% patients with obvious gastrointestinal bleeding complaint.[16] Other clinical manifestation which may be present is protein loss from intestinal mucosa inflammation process. Usually mild and may happen up to 16 months after the cessation of NSAIDs. Jejunum dysfunction in NSAIDs enteropathy may reveal cause diarrhoea symptoms, which resembles absorption disturbance in celiac disease. Disturbance in vitamin B12 and bile acid absorption may happen in ileum dysfunction.[2] Intestinal perforation has been reported to occur in long term use of NSAIDs (indomethacin), in patients with rheumatoid arthritis.[17] Small intestinal stricture also become a pathognomonic sign in NSAIDs enteropathy. The signature appearance of stricture is circumferential shape, fibrous, multiple (can reach dozens), thin (1-4 mm) and may cause severe intestinal obstruction.[2]

In patients with gastroenteropathy who experienced bleeding, there was also the presence of decreased haemoglobin and haematocrit level, also the presence of faecal occult blood. Hypoalbuminemia can also be found in 5-10% patients. Anaemia is found in 1-5% patients who received NSAIDs. Anaemia may happen as a result of chronic gastrointestinal bleeding, Fe and vitamin B12 deficiency, malnutrition, or appearance of anaemia in chronic disease.[3]

Increase of small intestinal permeability can also be detected in NSAID enteropathy. The frequently used marker is saccharide (lactulose, manitol), poly ethylene glycol, and radionuclide (51Cr-EDTA) which level is detected later in the urine after oral administration. This examination is not specific with sensitivity of 60-80%, but has low specificity value. Intestinal inflammation can be detected in 44-70% patients and may persist up to 16 weeks after NSAIDs cessation. This can be detected through the increase of Indium^{111} level in faeces or small intestine after intravenous administration. Other examination that could be used is calprotectin examination (protein produced by neutrophils, monocytes, and macrophages) in faeces, which showed the presence of migration of these cells into the intestine. This examination also has low specificity value.[2]

Invasive procedures are needed to confirm diagnosis. In NSAIDs gastropathy, fiber optic endoscopy examination to the upper digestive tract and radiography examination using barium can be performed.[3] Through endoscopy, lesion can be observed directly, and biopsy can be conducted as an additional examination. While enteroscopy examination can be used to detect lesion with direct visualization of the small intestine and performing biopsy. The presenting appearance may vary, ranging from mucosal oedema, erosion, bleeding, up to the presence of small intestinal stricture. Lesion is usually located in the distal ileum and caecum, caused by enterohepatic circulation and excreted slowly. The specific appearance is small-intestinal diaphragms, which is clinically marked by intestinal obstruction. Small-intestinal diaphragms are in the shape of multiple thin rings accompanied with mucosal and submucosal fibrosis. Capsule endoscopy examinations can also be used as a non-invasive procedure in NSAID enteropathy.[2,18]

Maiden et al, classified capsule endoscopy findings into 5 groups, including reddened folds, denuded area, red spots, mucosal breaks, and bleeding. While, Graham categorized it into red spots, small erosions, large erosions, and ulcers. Compared to capsule endoscopy, enteroscopy has superiority, which is therapy can be applied directly after the findings of bleeding lesion and its ability in performing histopathology examination, although this procedure is invasive and require long time.[2,20]

PREVENTIVE AND MANAGEMENT STRATEGIES IN NSAID GASTROENTEROPATHY

Based on literature review, there are several preventive and management strategies in patients with NSAIDs gastroenteropathy. The most general strategy being used is combining NSAIDs with gastroprotective drugs, use of COX-2 selective, and *H. pylori* eradication. However, there are several other therapy options that have been developed and some of them are still need further study.[1,4]

Combination of NSAIDs with Gastroprotective Drugs

- **Prostaglandin analog**
  Prostaglandin analog is given together in combination with NSAIDs to substitute the prostaglandin which synthesis is inhibited by NSAIDs. The type of preparation being used is misoprostol. [1,4] In a meta-analysis, misoprostol had been proven to decrease the incidence of gastrointestinal ulcer due to NSAIDs administration.[21] Misoprostol was significantly proven to decrease the incidence of gastric ulcer in acute or chronic administration of NSAIDs, while for duodenal ulcer only in long term use of NSAIDs.[1] In MUCOSA study, administration of misoprostol 200 mg four times per day showed decreased NSAIDs complication as much as 40%.[1]
- **Sucralfate/antacid**
  In addition to its effect in decreasing exposure of damaged mucosa towards gastric acid by forming protective gel (sucralfate) or neutralize gastric acid (antacids), both of these drugs were thought to induce several other gastroprotective mechanisms. Only few data showed sucralfate administration could prevent damage of the gastric mucosa in long-term use of NSAIDs. Although in a small study, sucralfate could be used in preventing short-term gastrointestinal complications due to the use of NSAIDs, a clinical trial by Agrawal failed to prove the benefit in administering sucralfate to prevent gastric ulcer compared to misoprostol. Uses of antacids were also quite disappointing. From several studies, antacids did not exhibit clinical effects particularly in long-term administration of NSAIDs.[1]
- **Gastric Acid Secretion Inhibitor**
  Acid may worsen the mucosal damage caused by NSAIDs use, increase proteolitic enzyme (pepsin) activity, and increase acidic NSAIDs absorption. H2 receptor antagonist and proton pump inhibitors (PPIs) may protect gastric mucosa not only through inhibiting gastric acid secretion, but also through antioxidant characteristic and decrease free radicals.[1] Before PPIs are available, H2 receptor antagonist is a standard therapy for NSAIDs associated peptic ulcer. Although proven to be effective in treating ulceration in the stomach, this drug does not have significant effect in gastric bleeding, therefore currently doubling the dose (famotidine 40 mg twice per day) can decrease the incidence in six months after gastric ulcer has developed.[1] While the formation of duodenal ulcer can be prevented and upper gastrointestinal symptoms can ameliorate in administration of H2 receptor antagonist. [1]
  The use of PPIs habeen proven to be effective compared to H2 receptor antagonist and currently has become the standard therapy for peptic ulcer and gastro-oesophageal reflux-disease (GERD). Omeprazole 20 mg once per day has been proven to be significantly more effective compared to ranitidine 150 mg twice per day or misoprostol 200 mg twice per day. In several studies, omeprazole had been proven to be more effective in decreasing dyspepsia symptoms due to NSAIDs and could be well tolerated in comparison to misoprostol. In a study, administration of lansoprazole was proven to be effective and superior compared to placebo, but not with misoprostol in preventing NSAIDs associated gastric ulcer. At the end of week 12 in the study, absence of ulcer were found in 51% patients from placebo group, 92% from misoprostol group, and 82% from lansoprazole group.[1] Administration of Esomeprazole, isomer-S of omeprazole, exhibited higher bioavailability and better effectivity in suppressing acid secretion compared to other PPIs.[20]
  In a study, it was proven that combination of PPIs and NSAIDs had similar effectivity in decreasing NSAID gastropathy compared to the use of COX-2 selective inhibitor. [21]
  Long-term use of PPIs is reported to be safe, because PPIs action is very specific and has rare adverse effects. Before administering PPIs in long term, *H.pylori* eradication needs to be conducted if it was suspected or there was evidence of infection by this bacterium. The weakness of PPIs, this drug cannot protect mucosal damage due to NSAIDs in the distal part of intestine (for example, colon).[1,4]

- **Administration of COX-2 selective Inhibitor**
  COX-2 selective inhibitor, in line with its name, is a group of drugs, which selectively inhibit COX-2 enzyme, thus have anti-inflammatory effect, but still maintain gastroprotective effects through COX-1 pathway. Celecoxib and rofecoxib are drugs from this group which are proven to be effective and are more superior compared to non-selective COX inhibitor to gastrointestinal complications.[4] In a study, celecoxib in comparison to combination of diclofenac and omeprazole had relatively similar ulcer bleeding incidence (4.9% *vs.* 6.4%).[1]
  Although COX-2 selective inhibitor decreased the toxicity effect towards gastrointestinal, there was increase cardiovascular risk due to myocardial infarct and thrombosis. COX-2 selective inhibitor inhibits blood vessels' prostacyclin production. *Prostacyclin* has vasodilation effect and inhibit platelet aggregation. Long term study of celcoxib (CLASS) and cardiovascular effect in rofecoxib (VIGOR) cause the use of these drugs to be controversial.[4] Second generation from "*coxibs*" such as valdecoxib, etoricoxib, lumaricoxib, and parecoxib, have higher selectivity towards COX-2. Based on a study report, it was proven that this drug group had higher effectivity in treating inflammation and pain, but its association with adverse effects of NSAIDs was still unclear.[1]
- ***Helicobacter pylori Eradication***
  Relationship between NSAIDs and *Helicobacter Pylori (H. pylori)* is still debatable. A meta-analysis revealed the presence of synergic role between NSAIDs administration and *H. pylori* infection in the incidence of peptic ulcer. Peptic ulcer is more common to occur in NSAIDs user with positive *H. pylori* positive (41.7%) compared to those who were negative (25.9%).[1] Konturek *et al* reported that H. pylori might disrupt gastric adaptation to aspirin, but *H. pylori* eradication alone did not decrease ulcer risk or dyspepsia symptoms in long term use of NSAIDs and not effective in preventing upper gastrointestinal tract bleeding. Effects of *H. pylori* in patients who do not use NSAIDs are significantly different compared to those who use NSAIDs. Therefore, it is advised that *H. pylori* examination is performed in all patients who are planned to receive long term NSAIDs.[4] Based on a study by Hawkey and Langman suggested *H. pylori* eradication was required before starting therapy with selective COX-2 inhibitor. This recommendation is different from patients who will use low dose aspirin, because it will increase the cost considering the number of patients using aspirin as prophylaxis of cardiovascular disease, but in patients with peptic ulcer history, this examination is still recommended.[1]

NEW THERAPY

- ***NSAIDs Prodrug***
  NSAIDs Prodrug is potential in increasing antioxidant effect, water solubility, and produce *nitric oxide* (NO) and *hydrogen sulphide* (H_2S). NO has gastroprotective characteristic through the increase of blood circulation, mucous production, and bicarbonate secretion in gastric mucosa. NO may also decrease neutrophil adhesion in blood vessels' endothelia. Therefore, currently new therapy *nitric oxide releasing* NSAIDs (NO-NSAIDs), is being developed. Administration of NO-NSAIDs does not interfere gastroduodenal mucosa. NO naproxen is reported to have higher anti-inflammatory and analgesic effect. NO aspirin is also reported to have better anti-thrombotic effect compared to conventional aspirin. *Hydrogen Sulphide Releasing NSAID* (H_2S NSAID) also has gastroprotective effect and may improve ulceration that has happened. Derivatives of naproxen, diclofenac, and indomethacin can produce H_2S.[1] NSAIDs effect in distal intestinal mucosa, as has been described previously, is influenced by enterohepatic cycle. Combination of this drug with bile may result in NSAIDs enteropathy. Addition of phosphatidylcholine (PC) in NSAID (PC-NSAID) has been reported to decrease the cytotoxic effect of NSAIDs.[10]
  Several studies have been conducted to find new NSAID, which has gastrointestinal protection without cardiovascular adverse effect. Prodrug diclofenac, 1-(2,6-dichlorophenyl) indolin-2-1, has been reported to decrease PGE2, COX-2 expression, and ulceration. Ibuprofen isomer R(-) is better in preventing gastrointestinal complication compared to isomer S(+) due to shorter half-life in the plasma.[1]
- **Dual COX/5-LOX inhibitors**
  Besides prostaglandin, leukotriene is also metabolized through the arachidonic avid pathway by lipoxygenase (5-LOX) enzyme. Leukotriene is an important inflammatory mediator other than prostaglandin. Based on experimental study,

cystenil leukotriene contributed in the damage of gastric mucosa through microvascular disturbance and decrease mucosal defence. Inhibition of COX enzyme increases leukotriene synthesis. Therefore, the use of COX/5-LOX inhibitors (licofelone) is developed to increase anti-inflammatory effect and decrease the adverse effects to the gastric mucosa. In an endoscopy study, it was reported that there was normal results after four weeks administration of licofelone 200 mg twice daily as much as 93%, licofelone 400 mg as much as 89%, and naproxen 500 mg twice daily as much as 37%.[22] In a double blind clinical study, gastroduodenal ulcer appear in 1.5% patients who consume licofelone 200 mg twice daily compared with 15,3% patients with naproxen 500 mg twice daily, while both have equal analgesic effect.[23] In controlling pain licofelone 200 mg twice daily also has the equal effect to celecoxib 200 mg once daily. Different from selective COX-2 inhibitor, licofelone showed gastroprotective effect when in concurrent use with low dose aspirin.[27] Other advantages of licofelone use compared to selective COX-2 is the anti-thrombotic effect and inhibition of thrombocyte aggregation.[25]

OTHER CHOICES OF THERAPY

- **Lactoferrin**
  A case report showed the ability of bovine colostrum to prevent gastric ulceration due to NSAIDs. Other study stated the role of human's recombinant lactoferrin in decreasing gastrointestinal bleeding due to NSAIDs and gastric ulcer. Lactoferrin (C-lobe) decreases the incidence of gastrointestinal inflammation and bleeding in the administration of NSAIDs and selective COX-2 inhibitors. This is because this molecule can bind to other free drug molecules.[1]
- **Metronidazole**
  Metronidazole is an antibiotic used to treat anaerobic microbial infection. Administration of metronidazole 800 mg/day may decrease inflammation and intestinal bleeding due to NSAIDs, however there is no influence towards intestinal permeability. Sensitive microbes towards metronidazole have chemoattractant effect to neutrophil in NSAIDs enteropathy. Other antibiotics have not been proven to decrease NSAIDs enteropathy. This is caused by the role of metronidazole is not only in intestinal bacteria, but also in inhibition of oxidative phosphorylation in mitochondria of intestinal cells.[26]
- **Sulfasalazine**
  Sulfasalazine is an anti-inflammatory drugs usually used in treating inflammatory bowel disease, including ulcerative colitis and Crohn's disease. This therapy is proven to decrease inflammation and NSAIDs bleeding. Although the role in NSAIDs enteropathy is still unclear, sulfasalazine may improve ileitis in long-term use of NSAIDs.[1] In the latest clinical study, mesalazine, an active form of sulfasalazine, has been proven to improve mucosal damage due to long term use of NSAIDs (naproxen). In this study 18 patients consuming naproxen in the long term underwent capsule endoscopy examination before and after four weeks of mesalazine administration, and proved that mesalazine might improve moderate to severe intestinal mucosal damage.[27]
- **Rebamipide**
  Rebamipide increases mucous production and synthesis of prostaglandin, which has gastroprotective characteristic. This drug also has anti-inflammatory effect and has antioxidant characteristic towards free radicals in the gastrointestinal. In a study, it was reported that rebamipide might decrease small intestinal damage caused by administration of diclofenac compared to placebo.[28] Rebamipide does not only improve mucosal damage in NSAIDs enteropathy, but also improve nutritional status.[29] In a systematic review and meta-analysis, rebamipide proved to be effective and safe in preventing damage in the gastroduodenal and low gastrointestinal due to NSAIDs.[30]
- **Probiotics**
  Several studies have been performed to evaluate the effect of probiotic in NSAID gastroenteropathy. In a study, *Lactobacillus casei*, could decrease small intestinal damage in the use of low dose aspirin in long term.[31] In a clinical study, it was also reported that probiotic use could decrease faecal calprotein level (used as a marker of intestinal damage) in patients using indomethacin.[32] However, clinical evidences regarding the role of probiotic in gastrointestinal protection are still weak.
- **Nutritional intervention**
  Several 'pharmaconutrients' can be used as a prophylaxis. The use of these pharmaconutrients has several benefits because they have lower risk compared to medications that have many

adverse effects. Lactoferrin recombinant has been available in the form of oral supplement and as have been described before, have anti-inflammatory, antioxidant, and bactericidal effects. Fish protein, hydrolysate, is a fermentation from fish products, also good for intestinal by improving disturbance of intestinal permeability due to NSAIDs. Glutamine, non-essential amino acids, is reported to be effective in preventing the increase of intestinal mucosa permeability in the short-term use of NSAIDs. Bovine colostrum contains growth factors (such as insulin like growth factor), immunoglobulin, and antimicrobial peptides. The use of bovine colostrum together with glutamine is effective in decreasing intestinal damage and bacterial translocation in the short-term use of NSAIDs.[11] In an animal study using mouse reported the administration of grape seed proanthocyanidin extracts (GSPEs) in the damage of gastric mucosa due to NSAIDs. High dose GSPEs had been proven to have gastroprotective effects to mucosal damage, which is suspected through antioxidant effect which it possess.[33]

CONCLUSION

Review regarding gastrointestinal and cardiovascular risk becomes an important factor in determining therapy. In patients who have to use long term NSAIDs, suitable regiment and prophylaxis strategies may be used to prevent gastrointestinal complication. Several new therapies have been developed, including the use of low toxicity anti-inflammatory drugs, such as NO- and H_2S- NSAIDs, and dual inhibitor COX/5-LOX showed quite significant decrease of toxicity. Selective COX-2 inhibitors, prostaglandin derivatives, PC-NSAIDs, and probiotics revealed protective effect to any damage of the intestinal mucosa due to NSAIDs. The use of other therapy in the preventive and management strategies of NSAIDs gastroenteropathy still requires further research.

REFERENCES

1. Becker JC, Domschke W, Pohle T. Current approaches to prevent NSAID-induced gastropathy – COX selectivity and beyond. Br J Clin Pharmacol 2004;58:587-600.
2. Tachecí I, Kopáčová M, Rejchrt S, Bureš J. Non-steroidal anti-inflammatory drug induced injury to the small intestine. Acta Medica (Hradec Králové) 2010;53:3–11.
3. Schellack N. An overview of gastropathy induced by nonsteroidal anti inflammatory drugs. S Afr Pharm J 2012;79:12-18.
4. Sinha M, Gautam L, Shukla PM, Kaur P, Sharma S, Singh TP. Current Perspectives in NSAID-Induced Gastropathy. Mediators Inflamm 2013;2013:258209.
5. Douthwaite AH, Lintott GAM. Gastroscopic observation of effect of aspirin and certain other substances on stomach. Lancet 1938;2:1222–25.
6. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta-analysis. Lancet 2002;359:14–22.
7. Singh G, Rosen Ramey D. NSAID induced gastrointestinal complications: the ARAMIS perspective—1997. Arthritis, Rheumatism, and Aging Medical Information System. J Rheumatol Suppl 1998;51:8–16.
8. Wallace JL, Vong L. NSAID-induced gastrointestinal damage and the design of GI-sparing NSAIDs. Current Opinion in Investigational Drugs 2008;9:1151-56.
9. Allison MC, Howatson AG, Torrance CJ. Gastrointestinal damage associated with the use of nonteroidal antiinflammatory drugs. N Engl J Med 1992;327:751–4.
10. Lim YJ, Chun HJ. Recent advances in NSAIDs-induced enteropathy therapeutics: new options, new challenges. Gastroenterol Res Pract 2013;2013:761060.
11. Peterson K, McDonagh M, Thakurta S, Dana T, Roberts C, Chou R, et al. Drug class review: nonsteroidal antiinflammatory drugs (NSAIDs). Update 4 final report. [cited 2013 Jan 7]. Available from: URL: http://derp.ohsu.edu/about/final-document-display.cfm
12. Berardi RR, Fugit RV. Peptic ulcer disease. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: a pathophysiologic approach. 8th ed. New York: The McGraw-Hill Companies 2011.
13. Wallace JL, Vong L. NSAID-induced gastrointestinal damage and the design of GI-sparing NSAIDs. Curr Opin Investig Drugs 2008;9:1151-6.
14. Wallace JL. NSAID gastropathy and enteropathy: distinct pathogenesis likely necessitates distinct prevention strategies. British Journal of Pharmacology 2012;165:67–74.
15. Klein M, Linnemann D, Rosenberg J. Non-steroidal anti-infl ammatory drug–induced colopathy. BMJ Case Reports 2011; 10: 3436.
16. Wallace JL, Denou E, Vong L, Syer S, McKnight W, Jury J, et al. Proton pump inhibitors and low-dose aspirin markedly exacerbate NSAID-induced small intestinal injury: link to dysbiosis? Gastroenterology 2011;140:S-87.
17. Sidhu R, Sanders DS, McAlindon ME, et al. Capsule endoscopy for the evaluation of nonsteroidal anti-inflammatory drug-induced enteropathy: United Kingdom pilot data. Gastrointest Endosc 2006;64:1035.
18. Park SC, Chun HJ, Kang CD, Sul D. Prevention and management of non-steroidal anti-inflammatory drugs-induced small intestinal injury. World J Gastroenterol 2011;17:4647-53.
19. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. The New England Journal of Medicine 1999;341:1888–99.
20. Yeomans ND, Hawkey CJ, Jones R. Esomeprazole provides effective control of NSAID-associated upper GI symptoms in patients continuing to take NSAIDs. Gastroenterology 2003;124: A107.
21. Ray WA, Chung CP, Stein CM, Smalley WE, Hall K, Arbogast PG, et al. Risk of peptic ulcer hospitalizations in users of NSAIDs with gastroprotective cotherapy versus coxibs. Gastroenterology 2007;133:790–8.

22. Palmer R, Bias P, Buchner A, Elsässer R. Licofelone (ML3000). An inhibitor of COX-1, COX-2 and 5-LOX, is associated with less gastric damage than naproxen and is similar to placebo in man. Gastroenterology 2002;122:A54.
23. Reginster JY, Bias P, Buchner A. First clinical results of licofelone (ML3000), an inhibitor of COX-1, COX-2 and 5-LOX, for the treatment of osteoarthritis. Ann Rheum Dis 2002; 61:116.
24. Buchner A, Bias P, Lammerich A. Twice the therapeutic dose of licofelone – an inhibitor of COX-1, COX-2 and 5-LOX – results in a significantly lower gastrointestinal ulcer incidence than naproxen in osteoarthritis patients, when administered with or without concomitant low-dose aspirin [EULAR 2003; abstract FRI0214]. Ann Rheum Dis 2003;62.
25. Tries S, Laufer S, Radziwon P, Breddin HK. Antithrombotic and platelet function inhibiting effects of ML3000, a new antiinflammatory drug with Cox/5-LOX inhibitory activity. Inflamm Res 2002; 51: 129–34.
26. Fortun PJ, Hawkey CJ. Nonsteroidal antiinflammatory drugs and the small intestine. Curr Opin Gastroenterol 2007;23:134-141.
27. Rácz I, Szalai M, Kovács V, Regőczi H, Kiss G, Horváth Z. Mucosal healing effect of mesalazine granules in naproxen-induced small bowel enteropathy. World J Gastroenterol 2013;19:889-896.
28. Niwa Y, Nakamura M, Ohmiya N, Maeda O, Ando T, Itoh A, et al. Efficacy of rebamipide for diclofenac-induced small-intestinal mucosal injuries in healthy subjects: a prospective, randomized, double-blinded, placebo-controlled, cross-over study. J Gastroenterol 2008;43:270-276.
29. Kurokawa S, Katsuki S, Fujita T, Saitoh Y, Ohta H, Nishikawa K, et al. A randomized, double-blinded, placebo-controlled, multicenter trial, healing effect of rebamipide in patients with low-dose aspirin and/or non-steroidal anti-inflammatory drug induced small bowel injury. J Gastroenterol 2014;49:239-44.
30. Zhang S, Qing Q, Bai Y, Mao H, Zhu W, Chen Q, et al. Rebamipide helps defend against nonsteroidal anti-inflammatory drugs induced gastroenteropathy: a systematic review and meta-analysis. Dig Dis Sci 2013;58:1991-2000.
31. H. Endo, T. Higurashi, K. Hosono. Efficacy of Lactobacillus casei treatment on small bowel injury in chronic low-dose aspirin users: a pilot randomized controlled study. J Gastroenterol 2011;46:894–905.
32. Montalto M, Gallo A, Curigliano V, D'Onofrio F, Santoro L, Covino M, et al. Clinical trial: the effects of a probiotic mixture on non-steroidal anti-inflammatory drug enteropathy – a randomized, doubleblind, cross-over, placebo-controlled study. Aliment Pharmacol Ther 2010;32:209–14.
33. Kim TH, Jeon EJ, Cheung DY, Kim CW, Kim SS, Park SH, et al. Gastroprotective effects of grape seed proanthocyanidin extracts against nonsteroid anti-inflammatory drug-induced gastric injury in rats. Gut and Liver 2013;7:282-9.

Correspondence:
Dadang Makmun
Division of Gastroenterology
Department of Internal Medicine
Dr. Cipto Mangunkusumo General National Hospital
Jl. Diponegoro No.71 Jakarta Indonesia
Phone: +62-21-3153957 Facsimile: +62-21-3142454
E-mail: hdmakmun@yahoo.com