# Gastropathy Due to Non-Steroidal Anti Inflammatory Drugs: Pathophysiology and Management

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## ABSTRACT

*Gastropathy refers to the damage of the epithelial cells of the gastric mucosa and disturbance of epithelial cell regeneration unaccompanied by inflammation. Gastropathy occurs due to irritation by chemical agents (such as non-steroidal anti inflammatory drugs – NSAIDs and alcohol), bile reflux, hypovolemic conditions, and chronic obstruction.*

*NSAIDs in general are chemical agents that cause irritation of the upper gastrointestinal tract through direct and indirect topical effects and by inhibiting prostaglandin synthesis through inhibition of COX-1 and COX-2. There are many data that demonstrates that the anti-inflammatory function of NSAIDs is mainly through inhibition of COX-2, while many of their side effects are due to inhibition of COX-1.*

*In general, there is a correlation between the influence of NSAID and the administered dose. The higher the dose, the higher the risk for upper gastrointestinal tract disorder. NSAID users who frequently switch drugs have a risk twice higher than those only receiving one kind of NSAID. Those who use NSAID with corticosteroids have 15 times the risk. Use of NSAID simultaneously with anticoagulants increases the risk of bleeding from ulcer 13 times compared to control subjects. NSAID use in a patient with history of bleeding from the gastrointestinal tract is 17.2 times non-users. Smoking also increases the percentage of gastroduodenal ulcer due to NSAID.*

*Clinical symptoms of NSAID gastropathy are often only dyspepsia syndrome. There is no correlation between symptoms and endoscopic findings.*

*The first step in the therapy of NSAID gastropathy is termination of NSAID administration. To treat and prevent risks of gastropathy due to NSAID, mucosal protection agents may be used. Out of the various kinds of medicine available, proton-pump inhibitors turn out to be more effective compared to H2 receptor antagonists or cytoprotective agents.*


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## INTRODUCTION

Gastropathy refers to damage of the epithelial cells of the gastric mucosa and disturbance of epithelial cell regeneration unaccompanied by inflammation. Gastropathy occurs due to irritation by chemical agents (such as non-steroidal anti inflammatory drugs – NSAIDs and alcohol), bile reflux, hypovolemic conditions, and chronic obstruction.[29]

Up to now, gastropathy due to NSAID is still a problem commonly discussed by experts. Especially since NSAIDs are widely distributed in the community unaccompanied by proper knowledge on their gastrointestinal side effects. We know that these gastrointestinal side effects may occur without or with minimal signs or symptoms. Thus, the condition has covertly grown out of hand due to the complications. Thus, it cannot be denied that therapy using NSAID may be very costly, particularly with the problem of gastropathy.

The indications for the use of NSAID have extended beyond its role as an anti-inflammatory agent to prophylaxis of myocardiac infarct and stroke. As these drugs are more frequently used, the possibility of gastrointestinal side effects also increases.[7]

It is estimated that 1 to 2% of patients who use NSAID for 3 months suffer from gastrointestinal ulceration. Bleeding and perforation is found in 2 to 5% of those using NSAID for 1 year.[11] A survey conducted by the Japanese Rheumatism Association in the year 1991 found that out of 100 patients with rheumatism receiving NSAIDs for 3 months, 15.5% suffered from gastric ulcer, 38.5% suffered from duodenal ulcer, and 1.9% to 2.7% suffer from duodenitis, even though some of these patients have received H2 blockers. From an endoscopic study on 41 patients, Yanagawa et al (1999) found 31

patients (73.8%) suffering from gastroduodenal mucosa lesions after 2 weeks of administration of sodium diclofenac.[27]

## THE INFLUENCE OF NSAIDS ON THE GASTER

Upper gastrointestinal disorder due to NSAID is caused by direct and indirect topical effects as well as inhibition of prostaglandin synthesis by NSAID. Lately, neutrophils were discovered to play a role in the pathogenesis of gastroduodenal ulcer due to NSAID. They apparently create an imbalance of gastroduodenal aggressive and defensive factors.[6,17]

Aggressive factors play a great role in the development of abnormal gastric juice and pepsin. While defensive factors are gastroduodenal mucosal defense consisting of mucus, bicarbonate secretion, endogenous prostaglandin, mucosal blood flow, H ion re-diffusion, and the ability of gastrointestinal epithelial cell regeneration. Mucus and bicarbonate cause epithelial cells to be resistant to damage, while increase mucosal blood flow increases oxygen and nutrition supply for the epithels and neutralization and re-diffusion of gastric juices and toxins.[29]

### A. Topical Effect

NSAIDs have topical effect on the gastric mucosa, where most NSAIDs are weak acids, thus would not ionize in the acidic environment of the gaster. Unionized NSAIDs easily freely diffuses through the cell membrane and quickly becomes concentrated in the gastric epithelial cell under normal conditions. Such condition increases the paracellular permeability, resulting in outward diffusion of hydrogen ions, and damage to the gastric mucosa.[6,11] NSAIDs cause damage to the mucus lining of the gastric wall that functions to minimize direct contact between the gastric wall epithelial lining and gastric contents.[7]

### B. Inhibition of Prostaglandin Synthesis

NSAIDs in general tend to stimulate the gaster and cause damage to the gastric mucosa by inhibiting prostaglandin synthesis, especially PGE1, PGE2, and PGI2. Prostaglandin is a rapidly disintegrating substance that works as a local hormone and plays an important role in the physiology or various pathologic processes.

The production of prostaglandin is ignited by phospholypase A2 that releases arachidonic acid. The arachidonic acid that is form is then broken down by cyclooxygenase enzyme into cyclic endoperoxydase that would then produce various types of prostaglandin. Prostaglandin ensures gastric mucosal defense by regulating the mucosal microcirculation, carbonic secretion, and adequate mucosal lining thickness. Prostaglandin then increases mucosal defense towards aggressive factors in the gastric lumen.[7]

There are two kinds of cyclooxygenase enzyme that plays a role in prostaglandin synthesis, as follows:

### 1. Cyclooxygenase-1 (COX-1)

This enzyme is found on almost all body tissues, including the gaster, intestines, platelet, bronchial mucosa, and kidneys. On these tissues, these enzymes maintain cell life. COX01, as a constitutive enzyme, produces PGI2 and PGE2 prostaglandin as well as thromboxane (TXA2) needed for hemostasis functions. Physiologically, these enzymes control vascular periopheral pressure, renal blood flow, sodium excretion, and renin secretion. These enzymes play a role in platelet aggregation. In the gaster, these enzyme is responsible for the production of prostaglandin which functions to protect gastric mucosa and regulate the bloodflow.[16,24]

### 2. Cyclooxygenase-2 (COX-2)

COX-2 are found in immune cells, blood vessel endothelial cells, and synovial fibroblasts. This enzyme can easily be induced by various mechanisms, and produces PGE2, which plays a role in inflammation, pain, and fever.[16] This enzyme is found in various inflammatory cells in low concentration. However, stimulation increases its level, particularly in leukocytes, monocytes, and chondrocytes.[7,24]

There are plenty of data that demonstrate that the anti-inflammatory functions of NSAIDs are mostly through COX-2 inhibition, while most of the side effects of NSAIDs are due to the inhibition of COX-1. Almost all NSAIDs in the market today inhibits both COX-1 and COX-2, even though at different degrees.[12]

COX-1 suppression by NSAIDs increases the production of gastric acid, suppresses the secretion of gastric bicarbonate, prostaglandin, and gastric mucosal cell proliferation, thus disturbing the normal gastric protection mechanism.[24] This can be seen through the use of aspirin daily for 3 months. The use of aspirin significantly reduces the level of prostaglandin approximately 40%. It also significantly injures the gastric mucosa.[3]

By inhibiting the COX-2 enzyme, NSAIDs reduces prostaglandin synthesis, which is an important mediator in the inflammatory process, thus alleviating inflammatory symptoms such as edema and function loss.[12,24]

Rofecoxib, a drug that more specifically inhibits COX-2, reduces the synthesis of prostaglandin E2 at the

antrum mucosa 18% compared to Naproxen, that reduces it to 65%.[25] While compared to ibuprofen, it turned out that after 24 weeks of treatment, 9.6% of patients receiving 25 mg of rofecoxib and 14.7% of patients receiving 50 mg of rofecoxib suffered from gastroduodenal ulcer. Out of the patients receiving ibuprofen, 45.8% suffered from gastroduodenal ulcer.[14]

### C. The Role of Neutrophils

It has been known for a while that neutrophiles play a role in the pathogenesis of gastropathy due to NSAID use. Evidently, NSAID increases neutrophil adherence on the microvascular endothel, and increases prostacyclin synthesis from the endothel, with a strong anti-adhesive character.[6] Neutrophil adherence on the gastric vascular endothel is the result of increased endothelial release of intracellular adhesion molecule 1 (ICAM-1).[18]

Neutrophil adherence on the vascular endothelium causes partial occlusion of the microcirculation. Afterwards, there is a reduction of gastroduodenal mucosal blood flow, which is a predisposition to various mucosal injury due to intraluminal factors such as gastric acid.[6,7,18] On the other hand, neutrophil activation also releases free radicals and protease that damages the mucosal tissue.[6,7]

Taha, et al (1999), based on a study on 120 patients receiving non-steroidal anti-inflammatory drugs concluded that increased gastric mucosal nutrophil increases the incidence of ulceration in long-term use of NSAIDs.[23]

## RISK FACTORS FOR THE DEVELOPMENT OF GASTROPATHY

Even though there is an evident correlation between the incidence of gastroduodenal mucosal erosion and the use of NSAIDs, not all NSAID users suffer from disturbance gastroduodenal mucosa.[6] Various factors have been evaluated the correlation with the possibility of gastropathy. However, up to now, the predisposing factors for the development of gastroduodenal ulcers or other complications still cannot be fully explained.[6,7]

The result of these studies demonstrate that short-term as well as long-term use of NSAIDs both pose a risk of gastrointestinal bleeding. In general, there is a correlation between the effects of NSAIDs with the dosage administered. The higher the dose, the greater risk for upper gastrointestinal bleeding. This is also the case for those who use different kinds of NSAIDs or more than one type of NSAIDs. These patients have twice the risk of those receiving one type of NSAID.[11]

Age is estimated to be a risk factor for gastroduodenal ulceration. The risk of upper gastrointestinal tract bleeding in patients over 60 years of age is 13.2, compared to 2.8 in ages below 60 years. Bakowsky, et al, found the greatest risk factor in patients over 60 years of age (74%).[2] This may be due to a lower concentration of prostaglandin in the gaster and duodenum due to age.[4]

Case control studies generally estimate a 3-5 times increase in the incidence of bleeding or ulcer perforation in NSAID users compared to non-NSAID users. While the use of NSAIDs and corticosteroids simultaneously increases the risk 15 times. The use of NSAIDs with anticoagulants increases the risk 13 times compared to control subjects. The use of NSAIDs in those with a history of ulcer increase the risk of gastrointestinal bleeding 17.2 times compared to non-users. From various studies, there is a difference in NSAID toxicity, where ibuprofen is considered the lowest, followed by fenoprofen, aspirin, diclofenac, indomethasine, and pyroxicam.[7]

The study by Fiedman et al demonstrated that smoking also increases the incidence of gastroduodenal ulcer in NSAID users. Compared to non-smokers, the incidence in patients is 2.1 times in males and 1.6 times in females. The length of smoking, the amount of cigarettes consumed, as well as inhalation of cigarette smoke is also associated with increased gastropathy due to NSAID.[6]

Up to now, various factors are believed to be able to increase the risk of gastropathy in NSAID users. These factors are as follows:[6,7,22]

1. Old age (>over 65 years)
2. History of peptic ulcer, gastric bleeding
3. The use of steroid with NSAID
4. Female
5. The administered dose of NSAID
6. The length of NSAID use
7. Smoking
8. Alcoholism

## CLINICAL FINDINGS

Complaints of NSAID gastropathy often take the form of dyspepsia syndrome. The most common symptoms are pain or discomfort in the epigastric region, possibly accompanied by gassiness, nausea, vomiting, even generalized abdominal discomfort. There are also many cases of upper gastroduodenal bleeding due to NSAID use.[7,17] Po, in a study on 346 patients with rheumatism treated with NSAIDs for 2 months, discovered that 44% of patients complained of symptoms of dyspepsia, and 43% of those suffering from ulcer had no complaints.[19]

Symptoms of dyspepsia are more commonly found in patients with normal endoscopy (19%) compared to those with abnormal endoscopic findings (9%).[15]

Another author reported that 30-40% of gastropathy due to NSAID use are found with no symptoms, even though endoscopic examination demonstrated acute gastroduodenal mucosal lesion.[17]

Thus, there is no correlation between complaints and endoscopic findings in patients with NSAID gastropathy. Complaints may be absent even though endoscopy demonstrated ulceration, and vice versa. Thus, even with a complaint of dyspepsia in the use of NSAID, the drug should be terminated due to a predicted high risk for NSAID gastropathy. Patients with a high risk of acute lesion of the gastric mucosa should use NSAID with caution, especially in using more than one kind of NSAID or in combination with steroids.[7]

## TREATMENT AND PREVENTION OF GASTROPATHY

If NSAID treatment has resulted in gastropathy, gastroscopy should be conducted to establish the definite diagnosis, since there is no correlation between complaints and gastroscopic findings. There could be a lack of complaints, even though endoscopy demonstrates ulceration, and vice versa.[7,17]

### A. Treatment of Gastropathy

The initial treatment of gastropathy due to NSAID is the termination of NSAID administration. Termination of NSAID facilitates healing with the use of conventional medications.[7] administration of 300 mg of ranitidine at night for 6 weeks in patients with NSAID gastropathy demonstrates satisfactory results.[10] Compared to ranitidine, omeprazole turned out to be more effective in healing gastric ulcer due to NSAID.[19,30] Omeprazole is also better than sucralphate.[20] Administration of 40 mg of famotidine twice daily for 12 weeks with the termination of NSAID use can heal NSAID gastropathy.[11]

Po reported that administration of 800 micrograms of misoprostol daily for 4 to 8 weeks can heal gastric ulcer due to the use of NSAID up to 67% and 75%.[19] Other authors use 50 mg of teprenon 3 times daily after meals. Two weeks of treatment demonstrate a significant reduction of mucosal erosion level.[21]

### B. Prevention of Gastropathy

NSAIDs are still commonly used, particularly for cases of arthritis. However, its use should be carefully considered, particularly for cases with risk of gastropathy. To suppress the risk of gastropathy due to NSAID, NSAID should be used with clear indication, to achieve optimal benefits with the smallest most effective dose.[7,16]

In patients that need NSAIDs, we should theoretically find an NSAID that only suppresses COX-2 at the site of pain, without suppressing COX-1 in the gaster. There is adequate reason to avoid chronic use of NSAID in patients over 60 years of age and history of gastroduodenitis or upper gastrointestinal bleeding. Another effort would be administration of NSAID with mucosal protection agents. We know the need to maintain balance between defensive and aggressive factors.[6,7,13]

#### 1. H2 Receptor Antagonists

These drugs inhibit basal and nocturnal gastric acid secretion. In addition to preventing the side effects of NSAIDs on the gaster, it is also beneficial to treat gastropathy due to the administration of NSAIDs.[10] Famotidine reduces the incidence of gastropathy due to the use of NSAIDs.[23] Administration of 150 mg of ranitidine daily along side with NSAIDs significantly inhibits the formation of ulcer compared to placebo.[27]

#### 2. Proton-pump Inhibitors

Proton-pump inhibitors inhibit H, K, -ATPase action at the parietal cell for acid secretion. Thus, H ion exchange from the cytoplasm into the secretory canaliculi does not occur and chloride acid in the canaliculi does not occur.[10] Administration of 20 mg of omeprazole with the use of NSAIDs for 3 months prevents the formation of ulcer.[5,8]

#### 3. Cytoprotective Agents

Cytoprotective drugs greatly facilitate the healing of ulcer and prevention of the development of ulcer. These drugs increase the production of PGE2, increase mucus and bicarbonate secretion to increase the cytoprotective capability of the mucosa.[9] Teprenon,[28] as well as cetraxate,[26] prevent gastric abnormality due to the use of NSAID. While the use of sucralphate to prevent gastrointestinal disorder is not as effective as the use of misoprostol.[22]

#### 4. Prostaglandin Analog

This drug stimulates the secretion of bicarbonate and produces the mucus of the gastrointestinal mucosa, increases mucosal blood flow, and renews damaged epithelial cells. At therapeutic dose, this patient reduces basal secretion of gastric acid as well as that after stimulation.[9]

Administration of 200 micrograms of misoprostol in

combination with 50 mg of diclofenac is an alternative to the prevention of the side effects of NSAIDs of the gastrointestinal tract. The bioavailability of combined misoprostol and diclofenac results equivalent to separate administration of either misoprostol or diclofenac. The combination of these two drugs also produces equal results to separate administration of NSAIDs in alleviating symptoms of arthritis.[13,19,27] However, the use of misoprostol is also accompanied by disturbing side effects, particularly in the elderly. This drug should not be used by pregnant women.[22]

## CONCLUSION

1. Gastropathy refers to damage of the epithelial cells of the gastric mucosa and disturbance of epithelial cell regeneration unaccompanied by inflammation.
2. NSAID gastropathy is caused by the irritation of the upper gastrointestinal tract through direct and indirect topical effects and by the inhibition of prostaglandin synthesis by NSAIDs.
3. There is no correlation between symptoms and endoscopic findings.
4. To treat and prevent risks of gastropathy due to NSAID, mucosal protection agents may be used.
5. Out of the various kinds of medicine available, proton-pump inhibitors turn out to be more effective compared to H2 receptor antagonists or cytoprotective agents.

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