# Prevention of Acute NSAID-Induced Gastroduodenal Damage: Which Strategy is the Best?

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**Abstract**

Objectives: The aim of this review is to provide data on the efficacy of co-therapy of non selective NSAIDs given for short periods of time with gastroprotective drugs in preventing severe gastroduodenal mucosal damage, and data on the acute effect of Cyclooxygenase-2 inhibitors on the gastroduodenal mucosa.

Methods: Randomized trials on the use of gastroprotective drugs published after 1985 were identified through Medline and references of clinical reviews.

Results: The combined data showed that co-therapy with misoprostol or proton pump inhibitors decreases non-selective NSAIDs-induced gastric and duodenal damage by 55% and 45% respectively, as compared to placebo. The prevalence of acute gastroduodenal injury caused by cyclooxygenase-2 inhibitors is similar to that caused by the combination of non selective NSAIDs and different gastroprotective drugs. Old age, use of multiple NSAIDs, H2-blockers, irrespective of H. pylori status raised as risk factors for acute NSAIDs induced gastroduodenal injury.

Conclusions: The use of gastroprotective drugs in patients requiring NSAIDS for short periods of time, or alternatively the use of cyclooxygenase-2 inhibitors is recommended in certain clinical conditions.

**MeSH Words**: NSAIDS, gastritis, gastroprotection

## Introduction

*The Clinical Problem*

A 65 year old woman with rheumatoid arthritis is referred to the Emergency Department with acute monoarthritis of the knee. She has been treated with methotrexate for the last year and the disease has been quiescent. The patient has ischemic heart disease and she is on low dose aspirin at a dose of 100 mg/day. She often complains of upper abdominal pain relieved by

food and antacids. After ruling- out septic arthritis what will be the best treatment modality for this patient? A review on the use of NSAIDs for short periods of time in patients with gastrointestinal risk factors is presented.

Co-administration of gastroprotective drugs, i.e. misoprostol, H2 blockers and proton pump inhibitors, during chronic treatment with NSAIDs has been demonstrated to be clinically useful for the prevention of gastroduodenal mucosal damage [1]. Administration of NSAIDsfor short periods of time, i.e. acute musculoskeletal injuries or acute inflammatory conditions is a very common practice in the Emergency Department. The purpose of the present study is to review the need and efficacy of different drugs in the prevention of acute NSAID-induced gastroduodenal mucosal damage.

**Material and methods**

Randomized trials on the use of gastroprotective drugs published after 1985 were identified through Medline and references of clinical reviews. Included were studies on the efficacy of misoprostol H-2 blockers and proton pump inhibitors (PPIs) in the prevention of acute severe NSAIDs induced gastroduodenal mucosal injury. Only studies dealing with patients, but not with healthy volunteers were included in the analysis. Patients took NSAIDs for a period of 4-30 days. The gastric and duodenal damage was evaluated by endoscopy. Only severe damage defined as the presence of bleeding, ulcers, or more than ten erosions, was included. We also searched the literature on randomized studies looking for the effect of cyclooxygenase-2 inhibitors (COX-2) on the gastroduodenal mucosa as compared to non-selective NSAIDs

**Table 1.** Prevalence of gastroduodenal mucosal damage in patients treated with non-selective NSAIDs

| Patients | Trials (number) | NSAID | Dosage (mg/d) | Patients (number) | Severe Damage (%) | | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | **Placebo** | **Treatment** | |
| **Gastric Damage** | | | | | | | |
| Misoprostol | 3 | 1 Not specified | | 759 | 15.6 | 3.6 | [2-4] |
| | | 1 Various | Various | | | | |
| | | 1 Various | Various | | | | |
| H2-Blockers | 5 | 2 Indomethacin | 150 | 856 | 19.7 | 12.8 | [5-9] |
| | | 3 Various | Various | | | | |
| PPI | 3 | 1 Not specified | - | 355 | 10.9 | 4.9 | [10-12] |
| | | 1 Various | Various | | | | |
| | | 1 Diclofenac* | 50-100 | | 28.5 | 0 | |
| *Mean* | | | | | *17.3* | *7.9* | |
| **Duodenal Damage** | | | | | | | |
| Misoprostol | 1 | 1 Various | 50-100 | 186 | 6.2 | 2.2 | [2-4] |
| H2-Blockers | 5 | 2 Indomethacin | 50-100 | 856 | 9.8 | 6.0 | [5-9] |
| | | 3 Various | Various | | | | |
| PPI | 3 | 1 Not specified | - | 355 | 6.8 | 2.1 | [10-12] |
| | | 1 Various | Various | | | | |
| | | 1 Diclofenac* | 50-100 | | | | |
| *Mean* | | | | | *8.0* | *4.8* | |

* Pantoprazole versus one-week H. pylori eradication.

**Results**

The pooled data shows that non-selective NSAIDs induced acute damage is more frequent in the stomach as compared to the duodenum (mean 17.3% vs. 7.9%, respectively). Co-therapy of NSAIDs and misoprostol or PPIs but not H2-blockers significantly decreases NSAIDs induced gastric and duodenal damage by 55% and 45% respectively, as compared to placebo (Table 1). The prevalence of acute gastroduodenal injury caused by cyclooxygenase-2 inhibitors is similar to that caused by the combination of non-selective NSAIDs and different gastroprotective drugs (Table 2).

**Discussion**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed all over the world. Gastroduodenal damage due to NSAID use is probably the most frequent drug-induced adverse event [16]. NSAIDs cause gastrointestinal side effects, ranging in severity from mild dyspepsia to gastric hemorrhage and perforation resulting in admission to hospital, surgery and death. Risk factors for NSAIDs induced gastroduodenal damage include: old age, use of high dose or multiple NSAIDs, concomitant use of low-dose aspirin and other antiplatelet drugs, steroids and warfarin [16].

It is known that NSAID-related peptic ulcer and its complications occur both in chronic and in recent NSAID users, especially in elderly subjects [17,18]. It has been reported that over 50% of NSAID-induced gastroduodenal lesions occurred in patients who had taken NSAIDs in the seven-day period before endoscopy [18]. Moreover, it has been reported that recent NSAID use, for 30 or fewer days, was significantly associated with a bleeding complication in elderly peptic ulcer patients [19].

Standard protection against gastrointestinal toxicity induced by NSAIDs has entailed co-prescription of gastroprotective agents such as H2 receptor antagonists, proton pump inhibitors (PPIs) or prostaglandin analogues. Another protective strategy includes the use of COX-2 selective NSAIDs (i.e. etodolac) or COX-2 specific NSAIDs (i.e celecoxib, and others) alone.

Most of the data on NSAID-induced gastroduodenal damage as well as on the efficacy of gastroprotection comes from studies on patients who took NSAIDs regularly for more than one month [1]. Short-term studies comprise a minority, and a great number of these studies were performed in healthy volunteers. A meta-analysis of controlled clinical trials on prevention of acute NSAID-related gastroduodenal damage showed that co-treatment with gastroprotective drugs was more effective in healthy subjects than in patients with arthritis [20].

As Emergency Medicine physicians, our main concern is the short-term administration of NSAIDs for conditions such as acute inflammation or acute pain. The present analysis shows that co-treatment with gastroprotective drugs is effective in the short-term prevention of severe non-selective NSAID-related damage. The mean reduction of severe gastric and duodenal damage was 55 percent and 45 percent respectively. Misoprostol was the most effective drug in reducing NSAIDs induced gastric injury while PPIs and misoprostol reduced duodenal damage by the same extent. The role of age, concomitant use of two NSAIDs, the presence of H. pylori and the use of gastroprotection are further discussed in the following studies.

Age over 60 years is a risk factor for NSAIDs induced gastroduodenal damage and its complications. Pilotto et al. (2000) conducted a study in patients over 60 years old who needed NSAIDs and who tested positive for H. pylori.

Patients on NSAIDs were randomized to concomitant therapy with pantoprazole 40 mg daily for one month or to one week eradication therapy for H. pylori. In the pantoprazole group, none of the patients developed severe gastroduodenal damage as compared to 28.5% in the eradication group [12]. In another, observational study, peptic ulcer disease was found in 48% of 289 patients older than 65 years of age undergoing upper endoscopy. All of them had taken NSAIDs regularly for a period not shorter than 7 days and not longer than 30 days previous to endoscopy. Ulcers were found in 50.9% of those subjects not treated with PPIs or

**Table 2:** Acute gastroduodenal damage from COX2-inhibitors as compared to non-selective NSAIDs

| Patients | Trials ($N^0$) | NSAID | Dosage (mg/day) | Patients ($N^0$) | Severe damage (%) COX2 | **Severe damage (%) Non-selective NSAID** |
|---|---|---|---|---|---|---|
| **Gastroduodenal damage** | 1 | Celecoxib vs Naproxen | 400mg vs 1g | 536 | 4 | 19 |
| | 2 | Valdecoxib vs Naproxen | 40 vs 1g | 238 | 0.8 | 20.1 |

treated with H2 blockers as compared to 14.28% of subjects treated with PPIs. In this study the risk of peptic ulcer was higher in acute than in chronic NSAIDs users [21]. As compared to data shown in Table 1, the prevalence of peptic ulcer in these two studies was higher than the mean gastric and duodenal NSAIDs related damage in the placebo group.

In another study, the risk of upper gastrointestinal bleeding in elderly users of aspirin and other NSAIDs was 7.87 (CI 4.90-12.60) in acute users and 3.97 (CI 2.27-6.96) in chronic users. In acute users, concomitant therapy with PPIs reduced the risk of bleeding compared with non-users, whereas co-treatment with H2 blockers was associated with a significantly higher risk of bleeding than in non users. This study confirms also previous data that concomitant use of two NSAIDs or NSAID plus aspirin increases the risk of bleeding. The presence of H. pylori was not significantly associated with an increased risk of bleeding [22]. This finding is in agreement with the previous report that H. pylori eradication is not sufficient to reduce the risk of gastroduodenal damage which is better prevented by continuous pantoprazole treatment. The pathophysiological characteristics of the ageing stomach may account for the increased risk of bleeding during acute NSAID use, since adaptive processes of the gastric mucosa within the first month of treatment with NSAIDs are known to be significantly less functional in older subjects than in adults [23]. The increased risk of peptic ulceration and bleeding in this older population co-treated with H2-blockers, could be attributed to masking of warning symptoms [22].

The effects of COX-2 specific NSAIDs inhibitors on the gastroduodenal mucosa have been analyzed principally in patients treated for periods longer than six weeks [24,25]. Celecoxib in a dose of 400mg/day caused gastroduodenal damage in 4% of 270 treated patients as compared to 19% of 267 patients treated with naproxen 1g/day, during one month. Celecoxib-induced gastroduodenal damage was similar to that caused during co-treatment of non-selective NSAIDS and PPIs or Misoprostol. The results with valdecoxib are even better (Table 2), but the drug has been withdrawn last year because elevated risk of cardiovascular events and other side effects. In a recent systematic review it was concluded that COX-2 specific NSAIDs inhibitors significantly reduce the risk of symptomatic ulcers and probably reduce the risk of serious gastrointestinal complications, but data quality is low [26]. It seems logical that this finding will be similar for short term use.

In summary, all the strategies except H2 blockers are apparently protective of symptomatic ulcers

and against endoscopic ulcers. In the present review based on one study PPIs significantly reduced serious gastrointestinal complications. Still, should all individuals receiving NSAIDs for short periods of time be cotreated with gastroprotective drugs or specific COX-2 inhibitors? The answer is probably no. Suitable guidelines as recommended by several investigators include the following strategies [27]:

1. In patients without risk factors the least ulcerogenic conventional NSAID is recommended

2. In patients with moderate risk (one to two risk factors), the combination of a non-selective NSAID and misoprostol or a PPI. The other alternative is the substitution for a COX-2 inhibitor alone. There are no sufficient data comparing coxibs and NSAIDs combined with either PPI or misoprostol, therefore the relative risk-benefit of these two strategies in high risk patients still remains unknown. The cost benefit of each strategy is different in different countries.

3. In patients with high risk (concomitant low-dose aspirin, steroids or anticoagulants) the combination of a COX-2 inhibitor, low dose aspirin (<100 mg) and a PPI or misoprostol are recommended.

4. Very high-risk patients (prior ulcer complications) should avoid NSAIDs

The patient described in the vignette meets the criteria for high risk patients: age, concomitant low dose aspirin and a clinical history suggestive of a peptic ulcer disease. A PPI in combination with a NSAID will be a suitable option.

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