

# Analgesics and the gastrointestinal tract – What the pharmacist's assistant should know

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## ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used. Gastrointestinal adverse events are the most common side effects associated with NSAIDs and may be severe, even fatal. This article will review strategies for minimising the risk of NSAID-related gastrointestinal events such as identifying patients at increased risk, assessing the rational choice and use of NSAIDs and cyclo-oxygenase 2 (COX-2) inhibitors and determining when it is appropriate to use gastroprotective agents such as misoprostol or proton pump inhibitors.<sup>2</sup>

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently used class of medicines worldwide. They are effective anti-pyretic, analgesic and anti-inflammatory agents. NSAIDs are used for both acute conditions such as headache, menstrual pain, fever, toothache and muscular aches and pains and chronically for the management of osteoarthritis and rheumatoid arthritis. Aspirin is also used chronically as an anti-thrombotic agent for cardiovascular protection in patients at high risk of cardiovascular disease.

NSAIDs are generally well tolerated.<sup>4</sup> However, they are associated with a significant risk of gastrointestinal (GI) side effects ranging from superficial irritation or damage with minor symptoms such as dyspepsia, abdominal pain and diarrhoea to severe events including duodenal and gastric ulcers and potentially fatal ulcer complications such as GI bleeding and ulcer perforation.<sup>1,4,5</sup> NSAIDs are therefore contraindicated in patients with active peptic ulcer disease and should be used with caution in the elderly.<sup>5</sup>

Although NSAIDs are associated with serious side effects many patients require NSAID therapy for effective pain management. The potential benefit of treatment must be weighed against the risks in each case.

## Pathogenesis of GI toxicity

NSAID-induced mucosal damage is caused by both local and systemic effects.

- Local effect: NSAIDs are weak acids and may directly irritate the gastric mucosa.<sup>3</sup> It is generally recommended that NSAIDs are taken after food to reduce this local irritation.
- Systemic effect: is the major cause of mucosal damage and is due to the post-absorptive inhibition of cyclo-oxygenase-1 which is responsible for the production of mucosal prostaglandin which protects the GI mucosa.<sup>5,7</sup> Intravenous and intramuscular administration of NSAIDs can also cause gastric or duodenal ulcers.<sup>7</sup>

## Incidence of GI adverse events

Finding the true incidence of GI side effects due to NSAIDs is difficult.<sup>5</sup> Up to 60% of

patients taking NSAIDs experience symptoms of dyspepsia.<sup>5</sup> In patients taking NSAIDs chronically, up to 25% will experience ulcer disease and of these 2-4% will experience ulcer complications.<sup>1,2</sup> The mortality rate in patients who develop ulcer complications is high, particularly in elderly patients.<sup>6</sup>

## Risk factors for serious GI events

Not every person is at equal risk. The assessment of a patients' risk factors is an important step in identifying patients who are at increased risk so that protective measures can be implemented.<sup>1-3</sup> There are several risk factors, both patient and drug related. See Table 1. The strongest risk factor is prior ulcer disease with a history of ulcer complications.<sup>2</sup>

Patients may then be stratified into risk groups:<sup>1,2</sup>

- low risk (no risk factors)
- moderate risk (one or two risk factors)
- high risk (multiple risk factors or a history of ulcer complications or concomitant use of corticosteroids or anticoagulants)

According to the MUCOSA study, the estimated annual incidence of NSAID related ulcer complications was<sup>2</sup>:

- 0.8% for patients without risk factors
- 2% for patients with one risk factor
- 7.6-8.6% for patients with three risk

**Table 1:** Risk factors for serious GI events

Drug factors
<ul style="list-style-type: none"> <li>• Choice of NSAID</li> <li>• High dose NSAID</li> <li>• Prolonged use of NSAID</li> <li>• Two NSAIDs e.g. low dose aspirin + NSAID</li> </ul>
Patient factors
<ul style="list-style-type: none"> <li>• Previous GI event, especially ulcer complications</li> <li>• Advanced age</li> <li>• Chronic debilitating disorders, especially cardiovascular disease</li> <li>• <i>Helicobacter pylori</i> infection</li> <li>• Concurrent corticosteroid or anticoagulant use</li> </ul>

factors

- 18% for patients with four risk factors.

## Selecting the most appropriate NSAID

The most effective method to prevent NSAID-related GI events is to avoid NSAID use.<sup>4</sup> Non-NSAID analgesics, such as paracetamol, should be considered before recommending a NSAID, where possible. In single doses, NSAIDs have analgesic efficacy comparable to paracetamol, although regular full dosage NSAIDs have both a lasting analgesic and anti-inflammatory effect.<sup>5</sup>

When selecting an NSAID the following factors should be considered: efficacy,<sup>5</sup> toxicity, dose and duration of therapy.<sup>5</sup>

- **Efficacy:** Differences in anti-inflammatory activity between NSAIDs is small, but there are considerable variations in patient response.<sup>5</sup> About 60% of patients will respond to any NSAID, and of those who do not respond to one may well respond to another.<sup>5</sup> Pain relief starts soon after taking the first dose and a full analgesic response is normally seen within the first week of regular use. The full anti-inflammatory effect may not be achieved for up to three weeks.<sup>5</sup> These general timeframes should be considered before increasing the dose or changing the NSAID due to perceived low efficacy.
- **Toxicity:** The risk of side effects is not uniform among NSAIDs. A meta-analysis of trials of commonly used conventional NSAIDs concluded that indomethacin has the highest GI risk and meloxicam the lowest.<sup>3</sup> See table 2.

**Table 2:** GI toxicity of NSAIDs from highest to lowest

<p><b>Indomethacin</b>  <b>Naproxen</b>  <b>Diclofenac</b>  <b>Piroxicam</b>  <b>Tenoxicam</b>  <b>Ibuprofen</b>  <b>Meloxicam</b></p>
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- **Duration of use:** The administration of an NSAID for a short period of time (less than one week) in healthy people is unlikely to result in any significant gastroduodenal toxicity.<sup>7</sup> Gastroduodenal complications are most common within the first three months after initiation of therapy.<sup>7</sup>
- **Dose:** Studies have shown an increase in ulcer risk with high NSAID doses. See table 3. If there is inadequate pain control, the dose should be increased gradually and the patient counselled to monitor for side effects.<sup>6</sup> Patients should generally be prescribed the minimum effective dose for the shortest possible time.

**The role of *Helicobacter pylori***

Meta-analysis has shown that the risk of peptic ulcer bleeding was increased in patients taking NSAIDs who had a *Helicobacter pylori* infection.<sup>1</sup> All patients requiring NSAIDs with a history of ulcers should be tested for *H. pylori* infection and, if the infection is present, eradication therapy should be given.<sup>1,3</sup>

**Gastroprotective therapy:**

**Enteric coating** of the NSAID has not been shown to be effective in preventing NSAID-related gastric or duodenal ulceration.<sup>1</sup>

Two approaches to gastroprotection include:

1. Co-therapy of NSAID with:
  - misoprostol
  - proton pump inhibitor (PPI)
  - high dose histamine-2-receptor antagonist (H2RA)
2. Substituting the traditional NSAID for a COX-2 inhibitor

**Misoprostol:** is a synthetic analogue of prostaglandin E1, a compound normally secreted by gastric mucosa and is essential for protecting the gastric mucosa from chemical damage.<sup>4</sup> Misoprostol has been

shown to be effective in reducing the incidence of gastroduodenal ulcers in patients receiving NSAIDs. The largest study reported a 40% reduction in serious GI complications in elderly patients with rheumatoid arthritis taking misoprostol 200 mcg four times daily with their NSAID.<sup>1-4</sup> However, dose related diarrhoea and abdominal cramps occurred in more than 20% of users and often resulted in discontinuation of therapy. Lower dose misoprostol has the same side effect profile as PPIs and is equally effective.<sup>1</sup> Furthermore, misoprostol is contraindicated during pregnancy and should not be used in women of childbearing potential unless adequate contraceptive measures are in place.

**Histamine-2-receptor antagonists (H2RA):**

e.g. cimetidine, ranitidine and famotidine block the histamine receptors in the parietal cells of the stomach, thereby preventing histamine-induced acid secretion.<sup>1</sup> Standard doses of H2RAs are not effective for the prevention of NSAID induced gastric ulcers, although they may prevent duodenal ulcers.<sup>1,3</sup> Systemic reviews have shown that double dose H2RAs are effective in reducing the risk of NSAID induced gastric and duodenal ulcers seen endoscopically.<sup>1</sup> H2RAs are, however, significantly less effective than PPIs.<sup>1</sup>

**Proton pump inhibitors (PPI):**

e.g. lansoprazole, omeprazole, esomeprazole, rabeprazole and pantoprazole inhibit the gastric enzyme responsible for the final step in gastric acid secretion and are the most potent inhibitors of gastric acid secretion.<sup>5</sup> PPIs significantly lower the incidence of gastric and duodenal ulcers and their complications in patients taking NSAIDs or COX-2 inhibitors.<sup>1</sup> PPIs are the most widely used gastroprotective agents.

**Cyclo-oxygenase-2 inhibitors (COX2):**

e.g. celecoxib. COX-2 inhibitors are more selective and have improved gastric safety profiles.<sup>1</sup>

COX-2 inhibitors and traditional NSAIDs are equally effective in the management of pain in patients with osteoarthritis or rheumatoid arthritis.<sup>4</sup> COX-2 inhibitors are associated with significantly lower incidence of gastric and duodenal ulcers when compared to traditional NSAIDs.<sup>1</sup> This benefit is lost when the patient is taking concomitant low-dose aspirin.<sup>1</sup> Thus patients taking low dose aspirin require other anti-ulcer prophylaxis.<sup>6</sup>

The usefulness of COX-2 inhibitors has been reduced by their association with myocardial infarction and other thrombotic cardiovascular events.<sup>1</sup> COX-2 inhibitors are an option for patients at low cardiovascular risk.<sup>6</sup>

**Place of gastroprotective therapy**

Patients with one or more risk factors should be considered for gastroprotective therapy.<sup>1-4</sup> The ACG (American College of Gastroenterology) has recently published guidelines for the prevention of NSAID-related ulcer complications which include recommendations regarding the use of gastroprotective therapy according to the patients risk group. See table 4.

**Monitoring patients**

Monitoring patients can be difficult as the presence of abdominal pain does not always correlate with the severity of NSAID-induced GI effects.<sup>5</sup> Less than half of patients experience dyspeptic symptoms before experiencing a serious GI event.<sup>5</sup> Mild GI adverse events should be used as warning signs of the development of a more serious event and therapy should be stopped, switched or gastroprotective therapy could be introduced.

**Conclusion:**

Despite the availability of safe and effective gastroprotective measures, the incidence of serious NSAID-induced GI side effects remains high. Health professionals need to promote and implement measures to ensure the rational use of NSAIDs, including the selection of an NSAID with low GI toxicity, using the lowest effective dose for the shortest feasible time and through the use of risk assessment and stratification as key tools, identify patients who require gastroprotective agents. sapa

**References:**

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**Table 3:** Relative risks (RR) were observed in studies assessing GI toxicity relative to dose<sup>3</sup>

Low dose ibuprofen (RR 1.6)	High dose ibuprofen (RR 4.2)
Low dose naproxen (RR 3.7)	High dose naproxen (RR 6.0)
Low dose indomethacin (RR 3.0)	High dose indomethacin (RR 7.0)

**Table 4:** Summary of recommendations of gastroprotective mechanisms according to risk<sup>1</sup>

High risk patients (e.g. prior ulcer complications or multiple risk factors)	<ul style="list-style-type: none"> <li>• Should receive alternative therapy</li> <li>• If NSAID is absolutely necessary, use COX-2 inhibitor <b>plus</b> PPI or misoprostol</li> </ul>
Moderate risk patients (1-2 risk factors)	<ul style="list-style-type: none"> <li>• COX-2 inhibitor</li> <li>• NSAID plus PPI or misoprostol</li> </ul>
Low risk patients (no risk factors)	<ul style="list-style-type: none"> <li>• Rational use of NSAID</li> </ul>
Patients requiring NSAID who take low dose aspirin for cardiovascular disease	<ul style="list-style-type: none"> <li>• Naproxen <b>plus</b> PPI or misoprostol</li> </ul>