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Review

An update on nonsteroidal anti-inflammatory drugs and gastrointestinal risk.

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Abstract

Recommendations for the prevention of nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal ulceration and cardiovascular (CV) complications were recently made available through an initiative designed in collaboration with leading specialists in South Africa. The prevention of CV complications and NSAID-related ulceration are discussed in two articles for the purposes of this publication. The first article in this two-part series presented an update on NSAID-related CV risk. This is the second article, and provides an update on NSAIDs and gastrointestinal risk.

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Introduction

Prescribing nonsteroidal anti-inflammatory drugs (NSAIDs) has become increasingly complex. NSAIDs have long been recognised as a major cause of gastrointestinal complications, such as bleeding, perforation and obstruction.[1] The introduction of cyclo-oxygenase-2 (COX-2) selective inhibitors or 'coxibs' led to the hope that the anti-inflammatory action of nonselective NSAIDs could be dissociated from their gastrointestinal toxicity.[1] However, enthusiasm for coxibs waned because of an increase in serious cardiovascular (CV) events with the coxibs.[1] More recent evidence suggests that traditional NSAIDs, with the possible exception of naproxen, also increase CV risk.[1]

Healthcare professionals now have to consider a multitude of gastrointestinal and CV risk factors before prescribing NSAIDs.[1] Recommendations on the appropriate use of NSAIDs have been developed from different perspectives, including rheumatology, gastroenterology and cardiology.[1] The South African recommendations for the prevention of NSAID-related gastrointestinal ulceration and CV complications have been developed in collaboration with leading gastroenterologists and a cardiologist.

Gastrointestinal toxicity

The most common side-effects that limit the use of NSAIDs are gastrointestinal, although adverse events also occur in other organ systems, e.g. the kidneys and the liver.[2,3] NSAIDs are associated with a spectrum of upper gastrointestinal complications, ranging from endoscopic ulcers in 10-30% of patients, to serious ulcer complications in 1-2% of patients.[3] The relative risk of developing serious upper gastrointestinal complications varies with individual NSAIDs, ranging from 1.42 with celecoxib, to 14.54 with ketorolac, and is influenced by NSAID half-life and the dose of the NSAID.[3]

Concomitant use of low-dose aspirin for CV prophylaxis is common in chronic NSAID users, and increases the risk of mucosal damage.[3] Low-dose aspirin (defined as 75-325 mg daily), increases the risk of gastrointestinal bleeding by approximately two-fold, while the combination of low-dose aspirin, plus another NSAID, increases the risk of gastrointestinal bleeding by two- to four-fold.[4] Most studies that evaluate the gastrointestinal safety of NSAIDs have found that COX-2 selective inhibitors are associated with a lower risk of ulcers and complications than nonselective NSAIDs.[3] A 2008 review of randomised controlled trials and meta-analyses estimated that COX-2 selective inhibitors were associated with a 61% relative risk reduction in ulcer complications, compared with nonselective NSAIDs.[3] Therefore, the risk of upper gastrointestinal complications is also increased by COX-2 selective inhibitors, but to a lesser extent than nonselective NSAIDs.[5] However, the concomitant use of aspirin with a COX-2 selective inhibitor eliminates the latter's gastrointestinal benefits.[3,5]

In recent years, the effect of NSAIDs on the lower gastrointestinal tract has also begun to receive greater attention. Opinion has moved toward a focus on complications which affect the entire gastrointestinal tract.[3] Unlike NSAID-associated upper gastrointestinal bleeding, the burden, risk factors, pathogenesis and prevention of lower gastrointestinal bleeding that are associated with NSAID use are poorly understood.[6] Current evidence suggests that mechanisms leading to small bowel injury with NSAID use are distinct from those of the upper gastrointestinal tract.[6] In future, therapy may be needed to protect the entire gastrointestinal tract in high-risk patients on NSAIDs.[6]

Besides the choice of NSAID, there are a number of risk factors for NSAID-associated gastrointestinal injury[3] (Table I).

Risk stratification for gastrointestinal events

Gastrointestinal risk may be arbitrarily stratified into low risk, i.e. no risk factors; moderate risk, i.e. the presence of one or two risk factors; and high risk, i.e. multiple risk factors, a history of ulcer complications or concomitant use of corticosteroids or anticoagulants[9,10] (Table II).

The consensus opinion of most experts is that patients with a history of a recent complicated ulcer are at very high risk and should only be treated with NSAIDs using extreme caution.[10] It is best to avoid NSAID treatment altogether.[10] However, if a NSAID is deemed to be essential, then a COX-2 selective inhibitor, plus misoprostol or a proton pump inhibitor, should be used.[10]

Table I: Risk factors associated with upper gastrointestinal events[5]

Characteristic	Relative risk range
Age (≥ 60-75 years)	2-5.5
History of upper gastrointestinal symptoms	1.2-5.3
History of peptic ulcer	2.3-3.1
History of gastrointestinal bleeding	2.6-13.5
High-dose nonsteroidal anti-inflammatory drugs	7
Multiple nonsteroidal anti-inflammatory drugs	9
Concomitant low-dose aspirin	1.5-12.7
Concomitant anticoagulants	6.4-19.3
Concomitant corticosteroids	1.6-2.2
Concomitant selective serotonin reuptake inhibitors	6.3
Severe rheumatoid arthritis disability	2.3
History of cardiovascular disease	1.3-1.8
Helicobacter pylori-positive*	1.8-2.4

* Helicobacter pylori infection and nonsteroidal anti-inflammatory drug use
independently increase the risk of peptic ulcer and ulcer bleeding.[5] Two systematic
reviews have confirmed the benefit of H. pylori eradication in the primary prevention of
peptic ulcers in nonsteroidal anti-inflammatory drug users[7,8]

Table II: Risk stratification for gastrointestinal events[9,10]

Risk factors	Level of risk
None	Low
One or two	Moderate
Three or more risk factors	
A history of ulcer complications	
Receiving concomitant anticoagulants, including	
aspirin and antiplatelet drugs, e.g. clopidogrel, and	
anticoagulants, e.g. warfarin	High
Receiving concomitant corticosteroids	

Reducing gastrointestinal risk

Current treatment guidelines recommend that NSAID users with gastrointestinal risk factors are prescribed a COX-2 selective agent or a nonselective NSAID, plus concurrent gastroprotective medications.[9] Available gastroprotective agents include histamine-2 (H_2)-receptor antagonists, misoprostol and proton-pump inhibitors (PPIs)[3] (Table III). A growing body of data suggests that combining a nonselective NSAID with gastroprotection, such as a PPI, is at least as effective as the use of a COX-2 selective inhibitor alone in reducing the incidence of serious gastrointestinal events.[9]

PPIs are more effective than H_2 antagonists which do not provide sufficient §acid suppression at traditional doses to prevent most ulcers.[3] Compared with misoprostol, PPIs have not been shown to be more effective, but PPIs may be preferred when the tolerability and poor compliance issues of misoprostol are considered.[3] A more recent concept is that of further reducing gastrointestinal risk by combining a COX-2 selective agent with a PPI.[3] Studies have shown that the addition of a PPI to treatment with a COX-2 selective agent significantly reduces the absolute risk of endoscopic gastric ulcers.[3]

Despite current recommendations, observational studies suggest that as many as 60-80% of patients using NSAIDs who have a gastrointestinal risk factor, including those receiving concomitant low-dose aspirin, do not receive gastroprotection.[3] In addition, adherence to gastroprotective treatment, if prescribed, has been reported to be poor.[9] In one study, nonadherence, defined as NSAID use on < 75% of days covered by a prescription for the gastroprotective agent, was estimated at 37%.[9] It can be assumed that, based on the often asymptomatic nature of ulcers, a primary reason for nonadherence to a gastroprotective agent is the perceived lack of effect.[9] The prescription of prophylactic gastroprotection adds to the pill burden in these patients and may complicate their daily regimen.[9]

Fixed-dose combinations of NSAIDs and gastroprotective agents have emerged as a strategy for providing gastroprotection and improving patient adherence.[3]

Summary of gastrointestinal and cardiovascular recommendations

On the basis of recommendations for the prevention of NSAIDrelated gastrointestinal and CV complications, an algorithmic approach was developed to help manage patients requiring longterm NSAID therapy.[5]

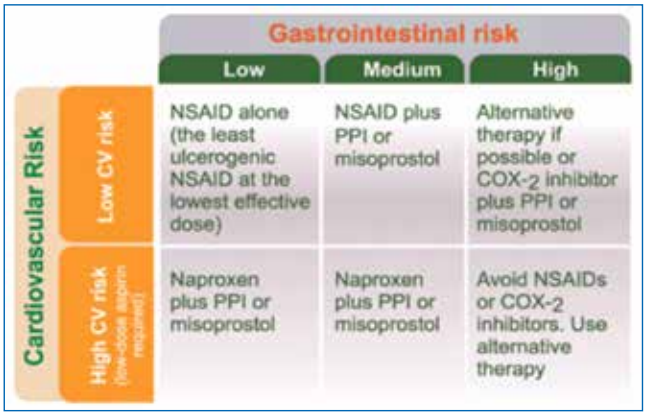
The approach is the following:

- The most important first step is to review the need for a NSAID, and to determine whether or not there are alternative approaches that can be adopted for that individual.[5]

Table III: Summary of recommendations for the prevention of nonsteroidal anti-inflammatory drug-related ulcer complications[10]

Recommended NSAID	Gastrointestinal risk		
	Low	Moderate	High
	Nonselective NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	Nonselective NSAID, plus PPI or misoprostol, or COX-2 selective inhibitor alone	Alternative therapy if possible, or COX-2 selective inhibitor plus PPI or misoprostol

COX-2: cyclo-oxygenase-2, NSAID: nonsteroidal anti-inflammatory drug, PPI: proton-pump inhibitor



COX-2: cyclo-oxygenase-2, CV: cardiovascular, NSAID: nonsteroidal anti-inflammatory drug, PPI: proton-pump inhibitor. Reproduced with kind permission from Schneider HR, Botha JF, Dalby AJ. Guidelines for prevention of NSAID-related gastrointestinal ulceration and cardiovascular complications. 2013.

Figure 1: Recommendations for the use of nonsteroidal antiinflammatory drugs based on gastrointestinal and cardiovascular risk[5,9-11]

- NSAIDs should always be used at the lowest effective dose, and for the shortest possible treatment duration.[5]
- The choice of NSAID and the need for gastroprotective and cardioprotective strategies for patients who require long-term NSAID therapy should be determined by a thorough assessment of CV and gastrointestinal risks. CV risk should be estimated, and managed according to appropriate CV guidelines, while the risk factors described in Tables I and II should be considered when determining gastrointestinal risk.
- A nonselective NSAID alone may be acceptable for patients with low CV and low gastrointestinal risk.[5]
- Naproxen plus a PPI or misoprostol is recommended for patientswith low gastrointestinal and high CV risk.[5] It should be notedthat high CV risk assumes the use of low-dose aspirin. Thus, agastrointestinal protective strategy is recommended.[5]
- A COX-2 inhibitor plus a PPI may offer the best gastrointestinal safety profile for patients with high gastrointestinal and lowCV risk.[5]
- NSAIDs and COX-2 inhibitors should be avoided and alternative therapy recommended when both the gastrointestinal and the CV risk is high.

Figure 1 provides recommendations for the use of NSAIDs, based on gastrointestinal and CV risk.[5,9-11]

Conclusion

It is clear that NSAIDs are associated with varying degrees of CV and gastrointestinal risk, and that individual NSAID and patient factors need to be considered in treatment decisions.[3] Pharmacists should play a role by ensuring that NSAIDs and COX-2 selective agents are used at the lowest possible dose, and for the shortest possible duration. It is also important to make sure that patients taking over-the-counter NSAIDs do not inadvertently double up on NSAIDs in cough and cold remedies, or when another prescription-only NSAID is prescribed by a doctor. Lastly, patients taking low-dose aspirin and a NSAID or a COX-2 inhibitor need gastroprotective medication, such as a PPI, to reduce their gastrointestinal risk.

References available on request