A review of nonsteroidal anti-inflammatory drugs

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Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) include the nonselective or traditional NSAIDs, as well as the cyclo-oxygenase-2-specific ones. These agents are most often used to manage pain associated with musculoskeletal conditions. The nonselective or traditional agents are still widely used, and are also freely available as over-the-counter analgesics. However, they carry the risk of serious cardiovascular, gastrointestinal and renal adverse effects, such as peptic ulcers and gastrointestinal bleeding, especially in patients who have a pre-existing high-risk profile. It is imperative that physicians are aware of these risk factors and choose agents that will provide the best benefit-to-risk profile, while taking into consideration the patient’s individual needs and risk profile.

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Introduction
Nonsteroidal anti-inflammatory drugs (NSAIDs) are used worldwide to treat pain and inflammation.1 However, in 2007, the American Heart Association published a warning in a focused update on the use of NSAIDs with respect to patients with established cardiac disease.2 The cardiovascular side-effects relating to the NSAIDs first became apparent in clinical trials that investigated the effects of selective cyclo-oxygenase-2 (COX-2) inhibitors. It has also been suggested in subsequent follow-up studies that there is an increase in cardiovascular risk in the nonselective NSAID group, e.g. ibuprofen and diclofenac. NSAIDs are still widely used across the globe and many of them can be purchased as over-the-counter (OTC) analgesics, e.g. ibuprofen, diclofenac, naproxen and mefenamic acid.3

Diclofenac was identified by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency as a high-risk NSAID in terms of its effects on the heart and circulation when administered systemically, i.e. capsules, tablets or injections.4 Individual drugs carry differing degrees of risk within the larger group of NSAIDs. Naproxen and low-dose ibuprofen carry the lowest cardiovascular risk, while diclofenac, at available OTC doses, carries a higher risk. The available data for etoricoxib (one of the cyclo-oxygenase inhibitors (coxibs) that are still available on the market) is still sparse, but it has a higher relative risk when compared to naproxen or ibuprofen. There are a range of gastrointestinal and central nervous system side-effects with indomethacin, and it has a cardiovascular risk profile similar to that of diclofenac.5 It is also well-recognised that there are severe gastrointestinal side-effects with NSAIDs, ranging from dyspepsia to gastroduodenal ulceration and bleeding.6

Cardiovascular effects

Physiology involved in the causation of cardiovascular adverse effects
Both isoforms of the COX enzyme, namely COX-1 and COX-2, are found in the blood vessels, stomach and kidneys.7,8 The normal action of COX-1 includes the physiological production and regulation of the prostanoids that are responsible for the maintenance of the following:7,8

- The gastrointestinal mucosa: Production of bicarbonate and mucus from the gastrointestinal mucosa, blood flow regulation and epithelial proliferation
- Platelet aggregation
- Renal prostaglandin synthesis: The two prostaglandins that are found in the kidneys are prostaglandin E2 (PGE2) and prostacyclin (PGI2). PGE2 is involved in sodium reabsorption in the thick ascending loop of Henle (in the nephron), as well as in the collecting tubules, and also seems to antagonise the antidiuretic effect of vasopressin on the latter.

COX-2 is expressed in the adult, mammalian renal cortex, the macula densa, the thick ascending limb of the loop of Henle, the interstitial cells in the inner medulla, and in the papillae and podocytes.7,8 COX-2 is detected upon stimulation in the monocyte, macrophage, neutrophil and endothelial cells.7,8 COX-2-release is triggered by cytokines, mitogens and endotoxins
in the inflammatory cells, and is responsible for prostaglandin production in inflamed tissue.7,8

**Cardiovascular events**

Individual factors may contribute to the relative risk of cardiovascular adverse events; underlying pathology, including pre-existing hypertension and renal impairment; and concomitant therapy, which may exacerbate the cardiovascular toxicity of the NSAIDs.9-11

Cardiovascular-related toxicity includes (Table I):9-11

- An increase in arterial blood pressure of approximately 4-6 mmHg, especially in susceptible individuals, i.e. those with known hypertension, or patients who are already on antihypertensive treatment
- New-onset congestive cardiac failure and the recurrence thereof
- Sodium and water retention that is primarily owing to the effects of COX-2. (COX-2 is produced by the cells of the macula densa. Inhibition can lead to sodium and water retention)

**Mechanisms involved in fluid retention, heart failure and hypertension**

These events may be owing to the presence of COX-2 in the kidneys and the effects of COX-1 in relation to the maintenance of a normal glomerular filtration rate (GFR) (Figure 1). Inhibition of these enzymes by the nonselective or traditional NSAIDs and selective COX-2 inhibitors results in renal effects, with varying degrees of sodium and water retention, depending on the agent in question.9 Some prostaglandins are synthesised in the kidneys and the disruption of their synthesis by the NSAIDs can result in acute renal failure, acute nephritis, electrolyte imbalances and reduced renal perfusion.7,9 The fluid retention might increase peripheral vascular resistance, with deleterious effects to the heart, including hypertension and heart failure. However, only a small proportion of patients who develop fluid retention eventually develop congestive heart failure.9,10

Within the group, there may be varying degrees of influence by the NSAIDs on blood pressure. Indomethacin is the most potent inhibitor of the prostaglandins, and is also associated with the highest incidence of heart failure. It provides great challenges
effective blood pressure control. The NSAIDs (both nonselective and selective) antagonise most of the important agents used to manage arterial hypertension, thus aggravating this condition.7,9

As stated previously, the cardiovascular risk profile of the NSAIDs differs among the various drugs, and currently naproxen appears to be the safer choice (Figure 2), particularly when compared to diclofenac, which presently carries a restrictive warning, especially when used in patients with an existing cardiovascular risk profile, such as high blood pressure, raised blood cholesterol, diabetes mellitus or smoking.6-7,9

A fixed-dose combination containing 500 mg of naproxen and 20 mg ofesomeprazole (Vimovo®) was introduced to the South African market towards the end of 2013. This product effectively combines the nonsteroidal, anti-inflammatory action of naproxen with a proton-pump inhibitor (PPI), so as to enable ease of use in patients who require NSAID therapy, with the addition of an effective gastroprotective agent. Currently, it is indicated in patients with inflammatory joint conditions, i.e. rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, who need proton-pump inhibition to reduce the incidence of NSAID-associated gastroduodenal ulceration.10-12

Naproxen has been established as the only traditional, nonselective NSAID, because it does not exhibit an increase in cardiothrombotic risk at its maximal dose of 1 000 mg per day. The fixed-dose combination tablet has been designed to contain a non-enteric-coated outer layer of esomeprazole for immediate release in the stomach, and an enteric-coated naproxen core for dissolution in the small intestine. Furthermore, with reference to its safety profile, the fixed-dose combination of naproxen plus esomeprazole has shown significantly improved gastrointestinal tolerability when compared to enteric-coated naproxen on its own, with significantly fewer gastric ulcers when compared to the latter.13-15

Erosive gastritis, dyspepsia, gastritis, diarrhoea, gastric ulceration, upper abdominal pain and nausea were commonly observed adverse reactions that were reported and associated during the conduct of clinical trials on the fixed-dose combination. It remains a recommendation, as for all NSAIDs and coxibs, that the lowest effective dose should be utilised, for the shortest possible duration, based on the patient’s individual treatment plan.14

Gastrointestinal effects

Pathophysiology of nonsteroidal anti-inflammatory drug-induced gastric damage and related toxicities

The NSAIDs, including aspirin, cause gastric mucosal damage in two very specific ways (Figure 3), namely:16

- Systemic inhibition of endogenous mucosal prostaglandin synthesis
- Direct or topical irritation of the gastric epithelium

\[92x756]Patients who require frequent or ongoing NSAID therapy

Assess:
- Cardiovascular risk profile
- Gastrointestinal risk profile

Risk factors for a cardiovascular risk assessment include:
- Established coronary artery disease
- Lose-dose, prophylactic aspirin therapy
- An estimated 10-year cardiovascular risk of > 20%

Risk factors for a gastrointestinal risk assessment include:
- Age ≥ 65-70 years
- Prior upper gastrointestinal event
- The concomitant use of aspirin, corticosteroids or anticoagulants
- Age ≥ 65-70 years
- A prior upper gastrointestinal event
- The concomitant use of aspirin, corticosteroids or anticoagulants

Figure 2: Management algorithm for frequent or ongoing nonsteroidal anti-inflammatory drug therapy4,7,9
The systemic inhibition of endogenous, mucosal prostaglandin synthesis is the result of inhibition of the COX enzyme. COX is the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins, and is inhibited by the NSAIDs. Two COX isoforms have been identified, namely COX-1 and COX-2 (Table II).

The side-effects associated with the NSAIDs are owing to the nonselective inhibition of COX-1, while their anti-inflammatory properties are because of the inhibition of COX-2. The nonselective or traditional NSAIDs, e.g. ibuprofen and diclofenac, inhibit COX-1 and COX-2, whereas the selective COX-2 inhibitors, e.g. celecoxib, are highly-selective inhibitors of the COX-2 isozyme.

So why is COX-2 still associated with adverse gastrointestinal outcomes? The original hypothesis was that selective COX-2 inhibitors would spare COX-1-mediated prostaglandins, and only inhibit the production of COX-2-mediated prostaglandins involved in the inflammatory process. However, COX-2 is actually involved in mucosal defence and repair, and it seems that both the COX isoforms are responsible for the physiological processes of tissue injury. It did not seem that the inhibition resulted in significant gastric damage in animal studies when COX-1 was selectively inhibited. In other studies in which selective COX-2 inhibitors were compared to nonselective or traditional NSAIDs for gastric complications, they produced severe gastrointestinal complications less frequently than the NSAIDs, but when compared to placebo, clinically significant gastrointestinal injuries appeared more frequently than those in the control group.

The addition of aspirin to a selective COX-2 regimen further reduces the benefit of the ulcer-sparing abilities and increases the ulcer risk. The use of clopidogrel and other medicines that impair...
Angiogenesis does not cause ulcers, but rather prevents the healing of gastric erosions that may lead to ulceration and bleeding. Angiogenesis is important for the repair of gastrointestinal mucosal disruptions. Furthermore, following the administration of NSAIDs, leukocytes (mostly neutrophils) tend to adhere to the vascular endothelium of the gastric microcirculation. This seems to be a critical event in the formation of gastric ulcers. When this step was inhibited in laboratory animals, it seemed as if the gastric ulcers were prevented.

However, neutrophil adhesion in the vascular endothelium contributes to NSAID-induced gastropathy in two ways, namely the:

- Physical obstruction of capillary blood flow
- Release of tissue-damaging proteases and oxygen-derived free radicals, once the neutrophils have been activated.

The inhibition of COX-2 induces neutrophil adherence when NSAIDs are administered. Thus, when a selective COX-2 inhibitor is administered, it may spare much of the total prostaglandin synthesis by the mucosa. It also triggers the key event in the pathogenesis of NSAID-induced gastropathy.

When comparing traditional NSAIDs and coxibs, celecoxib is known to cause less harm to the gastrointestinal tract because of the mechanism by which this drug selectively inhibits COX-2. Geriatric patients may still experience gastrointestinal intolerance (17%), although the occurrence is lower than that when using traditional NSAIDs (21-30%).

The topical irritant properties associated with the NSAIDs are mostly linked to the more acidic drugs, such as aspirin (Table III). This is because of their ability to decrease the hydrophobicity of the mucous gel layer in the gastric mucosa. Aspirin is the most damaging of all the NSAIDs, although most of them have topical irritant effects. Other formulations of NSAIDs, e.g. prodrugs, parenteral formulations, rectal preparations and enteric-coated aspirin, may be associated with less acute topical gastric mucosal injury, but may still be involved in varying degrees of gastrointestinal toxicity owing to their systemic inhibition of endogenous prostaglandins.

### Pharmacotherapeutical strategies for the prevention and treatment of nonsteroidal anti-inflammatory drug-related ulcers

**Identifying a risk profile for patients using nonsteroidal anti-inflammatory drug-associated gastrointestinal adverse events**

The risk of a NSAID-induced ulcer may be reduced by substituting the NSAID with a non-NSAID analgesic, such as paracetamol. This may not necessarily be feasible, especially in a patient with a severe, debilitating inflammatory condition, such as arthritis. Figure 4 depicts a possible algorithm for managing vulnerable patients on long-term NSAIDs, and those who also have cardiovascular risk factors. It illustrates the following basic principles:

- When a patient requires long-term NSAID therapy, the need for the NSAID should be reviewed and alternative approaches to treatment considered
- If no other alternative exists, the NSAID should be used at the lowest possible effective dose for the shortest possible period
- If the patient is going to be on long-term NSAID-therapy, a gastrointestinal and cardiovascular risk profile should be completed using the patient’s history, physical examination findings and laboratory investigations, as needed
- The lowest effective dose of aspirin should be initiated in patients with an increased cardiovascular risk
- Naproxen may be used in patients with a low gastrointestinal risk and high cardiovascular risk because it has the lowest cardiovascular risk profile in the group
- If a patient needs naproxen and aspirin, the addition of a gastroprotective agent, such as a PPI should be considered
- Testing for *Helicobacter pylori* in patients with a high-risk of NSAID-related gastrointestinal bleeding should be considered
- A COX-2 inhibitor and a PPI may offer good gastrointestinal protection in a patient who also has a very high risk of an upper gastrointestinal event. When a patient has both a high gastrointestinal and cardiovascular risk profile, then NSAIDs should be avoided. If this cannot be avoided altogether, then the physician should prioritise the cardiovascular and the gastrointestinal risks. If the gastrointestinal risk is the primary concern, a COX-2 inhibitor plus a PPI can be used. If the cardiovascular risk is the primary concern, then naproxen and a PPI should be considered, especially if the patient is already on aspirin.

### Table III: The minor and major gastrointestinal adverse effects of the nonsteroidal anti-inflammatory drugs

<table>
<thead>
<tr>
<th>Minor gastrointestinal effects</th>
<th>Major gastrointestinal effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia, nausea and heartburn</td>
<td>More serious gastrointestinal symptoms occur in the distal segment of the gastrointestinal tract, for example, diaphragm disease (a rare condition that is associated with the long-term use of NSAIDs). All NSAIDs are known to cause these effects. Minor effects are noted easily by the patients themselves, whereas major effects which occur with respect to the lower part of the gastrointestinal tract are not noted as readily. Limited options are available to control such serious effects</td>
</tr>
</tbody>
</table>

NSAIDs: non-steroidal anti-inflammatory drugs
**Other treatment options**

**Misoprostol**

Ulcer prophylaxis may be achieved by using misoprostol when the patient has to remain on NSAID therapy. As a synthetic PGE₁ analogue, misoprostol replaces the cytoprotective prostaglandins that are depleted by the NSAIDs from the gastrointestinal mucosa. The efficacy of misoprostol in preventing ulcers in patients using NSAIDs has been demonstrated in various studies, and proven to be above the use of placebo. Although the use of misoprostol has been demonstrated to reduce the risk of gastrointestinal events, it has also been proven to have its own spectrum of side-effects. Side-effects associated with the use of misoprostol include abdominal pain, nausea and diarrhoea, and it should be avoided in women of childbearing potential.

The side-effect profile and the frequent dosing needed with misoprostol makes compliance with therapy increasingly difficult, and comparative studies have shown that the PPIs may be more effective in patients with NSAID-induced gastric ulceration. A significant difference was not found between PPIs and misoprostol in preventing endoscopic ulcers in head-to-head studies that compared the PPIs to either low-dose or high-dose misoprostol. However, PPIs have proven to be superior in the prevention of duodenal ulcers.

A less frequent association with endoscopically diagnosed ulcers has been demonstrated with the fixed-dose combination of misoprostol and diclofenac (Arthrotec). The incidence of side-effects with misoprostol is dose dependent. However, reducing the dose reduces both the side-effects and efficacy.

**Sucralfate**

Sucralfate is a basic aluminium salt of sucrose octasulphate, which forms an adherent complex at the duodenal ulcer sites. It may be beneficial to use when treating NSAID-induced duodenal ulcers provided that the causative NSAID has been stopped. Sucralfate has not been shown to be effective in the prevention of NSAID-related gastric ulcers, and thus its routine use for this purpose is not recommended owing to the availability of superior therapeutic options.

**Histamine 2-receptor antagonists (cimetidine, ranitidine, famotidine and nizatidine)**

These agents act by competitive inhibition of the action of histamine at the histamine 2 (H₂) receptor site on the gastric parietal cell, thereby modulating gastric pH. Standard doses of the H₂-receptor antagonists (H₂RAs) may be effective in reducing NSAID-induced duodenal ulcers, but not gastric ulcers (the ulcer type most frequently associated with NSAIDs). The use of H₂RAs at higher doses, e.g. famotidine 20 or 40 mg twice daily, may reduce the incidence of gastric and duodenal ulceration. Having stated that, it is not recommended for these agents to be used routinely in asymptomatic patients receiving NSAIDs since this may mask dyspeptic symptoms associated with mucosal injury. PPIs have been demonstrated to be superior in healing gastroduodenal ulcers in patients using NSAIDs and are more effective in preventing ulcer recurrence.

### Figure 4: Algorithm for the use of nonsteroidal anti-inflammatory drugs in high-risk patients in terms of their gastrointestinal and cardiovascular risk profiles


**Table 4: Algorithm for the use of nonsteroidal anti-inflammatory drugs in high-risk patients in terms of their gastrointestinal and cardiovascular risk profiles**

<table>
<thead>
<tr>
<th>Gastrointestinal Risk</th>
<th>Cardiovascular Risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>A suitable nonselective or traditional NSAID</td>
</tr>
<tr>
<td>Low</td>
<td>High (on ASA)</td>
<td>Naproxen plus a PPI</td>
</tr>
<tr>
<td>Low</td>
<td>Very high</td>
<td>A COX-2 inhibitor alone or a nonselective or traditional NSAID plus a PPI</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>Naproxen plus a PPI</td>
</tr>
<tr>
<td>High</td>
<td>Very high</td>
<td>A COX-2 inhibitor plus a PPI</td>
</tr>
<tr>
<td>Cannot avoid NSAID</td>
<td>Very high</td>
<td>Naproxen plus a PPI</td>
</tr>
<tr>
<td>Avoid NSAID if possible</td>
<td>Very high</td>
<td>Naproxen plus a PPI</td>
</tr>
<tr>
<td>High (on ASA)</td>
<td>Low</td>
<td>A COX-2 inhibitor alone or a nonselective or traditional NSAID plus a PPI</td>
</tr>
<tr>
<td>High (on ASA)</td>
<td>High</td>
<td>Naproxen plus a PPI</td>
</tr>
</tbody>
</table>

**Notes:**
- **Rx:** treatment
- **ASA:** acetylsalicylic acid
- **COX-2:** cyclo-oxygenase-2
- **CV:** cardiovascular risk
- **NSAID:** nonsteroidal anti-inflammatory drug
- **PPI:** proton-pump inhibitor
- **Rx:** treatment
Proton-pump inhibitors (omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole)

PPIs bind irreversibly to the proton pump (H⁺-K⁺-ATPase), inhibiting basal and stimulated gastric acid secretion. They are administered as prodrugs that are activated in the acidic environment of the parietal cells. Lansoprazole has been proven to protect and heal the gastric mucosa following gastric damage induced by the NSAIDs. This is achieved via a novel mechanism of action, which uses an anti-apoptotic action mediated through regulating the factors involved in the mitochondrial and Fas-mediated death pathways of apoptosis. In addition to inhibiting acid secretion, lansoprazole also seems to offer gastroprotection through the inhibition of apoptosis and the stimulation of cell survival and proliferation. After 3-4 days of therapy, the degree of acid suppression increases as more of the proton pumps are inhibited. They only act on actively secreting proton pumps. Thus, they should be taken 30-60 minutes prior to having a meal.

The PPIs are available in various dosage forms and formulations, which include delayed-release, enteric-coated doses that have pH-sensitive granules in a gelatine capsule, rapidly disintegrating capsules and delayed-release enteric-coated tablets.

Similar healing times are seen in the five commonly available PPIs, i.e omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole, with similar maintenance times for ulcer healing and symptom relief, when used at the recommended dose.

In conclusion, the PPIs, especially when used as co-therapy to NSAIDs, reduce the risk of NSAID-induced gastric and duodenal ulcers, and are better tolerated than misoprostol. All of the PPIs are equally effective when used at standard doses, and they reduce the risk of NSAID-related ulcer bleeding. Chronic use of PPI therapy may be associated with an increased risk of infection and nutritional deficiencies as gastric acid plays a role in the defence against bacterial colonisation and nutrient absorption. Patients should be carefully monitored when using chronic therapy with the PPIs.

Cyclo-oxygenase-2 inhibitors (celecoxib and etoricoxib)

With concerns regarding their cardiovascular safety and the recent information on their related gastrointestinal toxicity, the use of COX-2 inhibitors should be evaluated on a case-by-case basis, with the risks carefully weighed versus the benefits for each patient. Celecoxib is no longer considered to be a truly selective COX-2 inhibitor as the same gastrointestinal warnings apply as those for the non-selective NSAIDs.

There seems to be a dose-dependent correlation in cardiovascular toxicity with celecoxib. The increase in cardiovascular toxicity appears to relate to the dose and duration of use. When using these agents, they should be given at the lowest possible dose, for the shortest possible duration. The gastric side-effects of the COX-2 inhibitors appear to be similar to those of the nonselective NSAIDs, namely dyspepsia, abdominal pain, fluid retention, hypertension and renal toxicity.

Renal effects

The pathophysiological role of prostaglandins in the kidney

The normal function of COX-1 in the kidney is to control renal haemodynamics and the GFR. The function of COX-2 affects water and salt excretion.

NSAIDs can cause both acute and chronic renal failure. Various forms of decreased renal function or renal failure have been observed.

A reduced glomerular filtration rate (GFR)

The GFR is indicative of damage to the renal system. When a patient presents with either acute renal failure (ARF) or chronic renal failure (CRF), a reduction in the GFR is noted.

Acute renal failure (ARF)

ARF is a rapid and sustained disruption of the normal kidney function which leads to an accumulation of waste products (urea and creatinine). ARF, as a potential side-effect of NSAID usage, is dose-dependent and reversible. The mechanism through which the NSAIDs can cause ARF is via their inhibition of the production of prostaglandins, and the resultant decrease in blood flow to the kidneys. Patients with a past history of heart failure, hypertension or diabetes mellitus have a higher risk of developing ARF, secondary to taking NSAIDs, than patients with normal renal function. The concomitant use of angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, the aminoglycosides and diuretics, pose an increased risk for the development of ARF.

Renal papillary necrosis

Renal papillary necrosis (RPN) is a kidney disorder that is characterised by the destruction of parts of, or all of, the renal papillae. NSAID-induced RPN is caused by the resultant lack of blood flow to the renal papillae, with the result that hypoxia occurs in these structures. Several of the NSAIDs, including celecoxib, can cause RPN, and the patient presents with high levels of urea and creatinine in the bloodstream.

Nephrotic syndrome with acute interstitial nephritis

NSAIDs can cause nephrotic syndrome, owing to their inhibition of COX that would normally increase the production of arachidonic acid cascade products. Patients with nephrotic syndrome can present with oedema, proteinuria, foamy urine, oliguria and haematuria. NSAIDs can also cause acute interstitial nephritis (AIN) owing to inflammation in the interstitial spaces between the kidney tubules, or because of hypersensitivity reactions to these drugs. AIN is a rare disease, is reversible, and may already be present within days of NSAID exposure.

Chronic renal failure (CRF)

NSAIDs can cause CRF owing to interstitial nephritis or papillary necrosis. Patients are at much greater risk of developing CRF if
they previously suffered from ARF. Any NSAID that is used on a chronic basis can potentially cause CRF in certain patients.19

Conclusion

The use of NSAIDs should be reserved for patients suffering from debilitating musculoskeletal conditions, e.g. osteoarthritis, and only when the benefit outweighs the risk. NSAIDS (nonselective and selective) should be used with caution in patients with pre-existing cardiovascular conditions, and the physician should select the NSAID with the lowest possible risk to the patient’s current condition, i.e. ensure that it is used at the lowest effective dose, and for the shortest possible period. It was once believed that only nonselective or traditional NSAIDs were the causative agents, but selective COX-2 inhibitors have now also been shown to be associated with untoward gastrointestinal side-effects. An individualised assessment of a patient’s current disease state and medication use is required to prevent NSAID-related ulceration. More importantly, the patient should be assessed for his or her degree of risk in terms of gastrointestinal, cardiovascular and renal toxicities.

References