

# Review of the safety of nonsteroidal anti-inflammatory drugs and selective cyclo-oxygenase-2 inhibitors

GS Tarr,<sup>1,2</sup> H Reuter,<sup>1,2,3</sup>

<sup>1</sup>Winelands Rheumatology Centre, Stellenbosch, <sup>2</sup>Helderberg Hospital Rheumatology Clinic, Somerset West

<sup>3</sup>Division of Rheumatology, Faculty of Medicine and Health Sciences, Stellenbosch University

**Correspondence to:** Helmuth Reuter, e-mail: [helmuth@reuter.co.za](mailto:helmuth@reuter.co.za)

## Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most common classes of medication used worldwide, and as the ageing population increases, the prevalence of painful arthritic conditions parallels this, resulting in the increased use of NSAIDs. Selective and nonselective cyclo-oxygenase inhibitors should be avoided, or at best used for short periods at the lowest possible effective dose, in patients with underlying atherosclerotic coronary disease.

**Keywords:** nonsteroidal anti-inflammatory drugs, NSAIDs, COX-2 inhibitors

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most common classes of medication used worldwide, and as the ageing population increases, the prevalence of painful arthritic conditions parallels this, resulting in the increased use of NSAIDs.

A systemic review found that NSAIDs were one of four drugs associated with the highest number of drug-related hospital admissions. The others were diuretics, anticoagulants and antiplatelet agents.<sup>1</sup> A wide range of adverse events are caused by both selective and nonselective cyclo-oxygenase (COX) inhibitors. Older patients are more predisposed to complications. Toxicity with use of these drugs has been noted since the development of phenylbutazone, an indoleacetic acid derivative; the first non-salicylate NSAID in the 1950s. Since then, based on improved knowledge on the synthesis and functioning of prostaglandins, drug development has facilitated greater anti-inflammatory effects and decreased toxicity, and has therefore boosted patient compliance.

## Mechanism of action

Inhibition of the COX enzyme, prostaglandin synthase, prevents the conversion of arachidonic acid to prostaglandins, prostacyclins and thromboxanes. There are two main isoforms of this enzyme, COX-1 and COX-2, whose expression varies in tissues. A third enzyme, COX-3, has been identified as a splice variant of COX-1, but its function and significance is not yet clear. COX-1 is a "housekeeping" enzyme, found in most tissues responsible for cellular processes, such as gastric protection, vascular homeostasis, platelet aggregation and kidney function. COX-2 expression only increases during inflammation, and is not detected in most tissues, except for the brain, kidney, bone and female reproductive system, under normal circumstances.

Other non-prostaglandin action by the NSAIDs includes the obstruction of neutrophil-endothelial interaction, thus decreasing chemotaxis;<sup>2</sup> nuclear factor kappa B inhibition<sup>3</sup> and being antinociceptive.<sup>4</sup>

In part, the degree of inhibition of a particular isoform affects the drugs activity and toxicity,<sup>5</sup> and this has become evident by considerable anti-inflammatory variability in individuals.<sup>6</sup> Reasons for variable drug effectiveness have been linked to their mechanism of action (prostaglandins synthesis inhibition or non- prostaglandin-mediated action), pharmacokinetics, pharmacodynamics and metabolism. Since there are six classes of NSAIDs, it is acceptable for a different class to be tried in the event of a two-week drug course failing to achieve the desired therapeutic result. This has never been studied in a prospective trial, nor is there current information linking the level of COX inhibition with effectiveness in individual patients.

Since the degree of NSAID activity varies from one person to another, it is plausible to consider that the extent of drug toxicity can also vary.

## Which is the safest nonsteroidal anti-inflammatory drug?

NSAIDs are fairly safe drugs to use if prescribed with caution, having taken into consideration the patient's risk factors and history to avoid unwanted drug complications.

Toxicity is as a consequence of their mechanism of action, i.e. the inhibition of prostaglandin synthesis, and therefore COX-1 inhibition is linked to higher degrees of gastrointestinal toxicity. The safety of COX inhibition and cardiovascular risk is a controversial issue, as well as whether or not the newer COX-2 selective NSAIDs are associated with a greater incidence of ischaemic heart disease and thromboembolic events in comparison to nonselective NSAIDs.

## Cardiovascular disease

A high risk of cardiovascular disease was highlighted when rofecoxib, a long-acting COX-2 inhibitor, was withdrawn from the market after a fivefold increased incidence of cardiovascular events was reported with this drug.

Unlike gastrointestinal toxicity, which can occur even after a short course of therapy, cardiovascular disease is normally associated with a longer duration of drug exposure.

The production of the vascular prostacyclin, PGI<sub>2</sub>, responsible for counter-acting thromboxane A<sub>2</sub> (TXA<sub>2</sub>) produced by the COX-1 enzyme, is an important function of the COX-2 enzyme. Therefore, PGI<sub>2</sub> is antagonistic to TXA<sub>2</sub>, which reduces platelet activation and causes vasodilation, and if this mechanism is lost through COX-2 inhibition, it predisposes to cardiovascular disease.

It is important to determine whether this cardiac risk only applies to those with existing cardiovascular disease or also to those without it. This was addressed in a 2013 meta-analysis of over 300 000 patients in 600 trials, assessed over one year, in which a placebo was compared with a nonselective COX inhibitor, i.e. diclofenac, ibuprofen or naproxen, or a COX-2 inhibitor. The primary end-point was the incidence of major cardiovascular events, i.e. nonfatal myocardial infarction (MI), a non-fatal stroke or vascular death, which were found to be significantly higher compared with placebo for high-dose diclofenac [adjusted rate ratio (ARR) 1.41] and COX-2 inhibitors (ARR 1.37), but not statistically significant for naproxen (ARR 0.93). The conclusion was that although there is an increased risk of approximately two events per 1 000 patient-years for diclofenac and COX-2 inhibitors, this is a small number, based on these patients' underlying cardiovascular risks (0.5% per year). According to this meta-analysis, naproxen was not associated with major cardiovascular events based on the available data, and seemed to be the safest NSAID for long-term use at a high dose.<sup>7</sup> Individuals who used naproxen were not at a lower risk of developing cardiovascular events than those using celecoxib in a study on 160 801 postmenopausal women who were enrolled into The Women's Health Initiative.<sup>8</sup> Concomitant selective COX-2 inhibitor use was no longer associated with an increased hazard of cardiovascular events in aspirin users.<sup>8</sup>

Patients with established cardiovascular disease have additional problems in that many of them may also be receiving antiplatelet, antithrombotic and/or oral anti-coagulant therapy, placing them at a higher risk of bleeding complications. A 30% increase in cardiovascular events and an approximate incidence of 11.2 events per 100 patient-years was reported in a recently published article from the Danish registry in which the risk of bleeding in patients with prior MI who were treated with both NSAIDs and antithrombotic medications was primarily investigated. The vast majority of cardiovascular events occurred in those treated with COX-1 inhibitors.<sup>9</sup> Only 8.5% of these patients experienced bleeding events.

The aforementioned incidence rate was higher than that reported in a systemic review in which it was concluded that the risk was 7-8 events per 100 patient-years, with very little difference between the COX-1 and COX-2 inhibitors, except for naproxen, which appeared to be slightly safer.<sup>7</sup>

It is not only the ability of NSAIDs to cause fluid retention which can exacerbate cardiac failure, and result in an elevation in blood pressure. Drug interference via vasoconstriction can also block the effects of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II-receptor blockers, and therefore minimise improvement in cardiac output and the diuretic effect.<sup>10</sup> Without a prior history of cardiac failure, the risk is very small, but there is a twofold increased risk using all NSAIDs compared to placebo,<sup>7</sup> and a dose-dependent increased risk of mortality (highest with diclofenac),<sup>11</sup> in those with existing cardiac dysfunction and a history of failure.

Isolated peripheral oedema is seen in 1-10% of patients, irrespective of whether COX-1 or COX-2 inhibitors are prescribed.

All anti-inflammatory medication, except for aspirin, can be associated with an increase in blood pressure and reduce the efficacy of antihypertensive medication, with the exception of calcium-channel blockers.

With the exception of aspirin, both COX-1 and COX-2 inhibitors have been associated with an increased risk (40-70%) of cardiac arrhythmias, specifically atrial fibrillation or flutter; probably highest with COX-2 inhibitors.<sup>12</sup>

## Gastrointestinal toxicity

Gastric prostaglandins, produced by the COX-1 enzyme, are responsible for mucosa cytoprotection by increasing glycoprotein (mucin), bicarbonate and phospholipid secretion by the gastric epithelial cells, as well as local vasodilation, thereby improving mucosal blood flow and oxygen delivery, and the increased restitution and proliferation of epithelial cells.

With the inhibition of COX-1 enzymes, these protective mechanisms are lost, predisposing to gastric and duodenal injury by acid and pepsin, which can ultimately lead to ulcer formation, complicated by bleeding and even perforation. Additional risk factors for gastrointestinal toxicity include being of advanced age, using a higher NSAID dose, a longer duration of therapy, a previous history of peptic ulcer disease and concomitant therapy, e.g. steroids, anticoagulants, antidepressants (specifically selective serotonin reuptake inhibitors), and bisphosphonates. Most complications are seen in the first three months, although there are very few in the first week after the initiation of COX-1 inhibitors.<sup>13</sup> It is important to remember that COX-2 inhibitors have reduced the incidence of gastric and duodenal events, but are not infallible as there is still slight COX-1 inhibition, and this can lead to gastric complications.<sup>14</sup>

Co-infection with *Helicobacter pylori* has also been shown to increase the risk of peptic ulcer disease, via independent and synergistic mechanisms.<sup>15</sup>

Nearly all NSAIDs may induce damage in the small and large bowel, but it is often subclinical. Varied results have been demonstrated in studies in which selective COX-2 inhibitors and nonselective NSAIDs have been compared. It is likely that COX-2 inhibitors are probably not more protective.<sup>16,17</sup> Bowel manifestations include iron deficiency anaemia from bleeding ulcers, enteropathy complicated by malabsorption and hypoalbuminaemia, bowel obstruction from strictures, and colitis and bowel perforation.

### Renal toxicity

In the kidney, there is a concentrated expression of the COX-2 enzyme in the *macula densa*, the thick ascending limb of the Loop of Henle, and the cortical collecting duct which upregulates during episodes of inflammation, making itself a target for NSAIDs. The prostaglandin produced herein acts to protect renal perfusion through afferent vasodilation during times of hypotension, counteracting the effects of angiotensin II, norepinephrine, vasopressin and endothelin, therefore minimising renal ischaemia and acute tubular necrosis.<sup>18</sup>

Renal injuries relating to NSAID use include electrolyte abnormalities, acid base disturbances, interstitial nephritis, tubular necrosis and progression to acute renal failure. There is a higher risk in individuals with already established chronic kidney disease, heart failure, volume depletion and hypercalcaemia, and on concomitant medication, such as radio-contrast exposure, aminoglycosides, amphotericin, diuretics, angiotensin-receptor blockers or ACE inhibitors.

Importantly, long-term NSAID use, excluding aspirin, has been associated with an increased risk of renal cell carcinoma.<sup>19</sup>

### Hepatotoxicity

Receiving liver function blood results with slightly elevated transaminases as a result of patients using chronic NSAIDs is not an uncommon finding. However, the progression to liver failure is rare, and this was evaluated in a retrospective study over four years on more than 600 000 patients who received over two million NSAID prescriptions. The risk of acute liver injury was found to be 3.7 patients per 100 000.<sup>20</sup> An interesting finding from these data was that patients with existing chronic inflammatory conditions, like rheumatoid arthritis, had a tenfold increased risk of developing liver injury, but this may also relate to concomitant immune-suppressive medication.

Like most other organ toxicities, withdrawing the NSAID results in complete recovery, and thus transient minor increases in liver enzymes have not been found to be a useful predictor of NSAID-associated acute liver injury.

### Pulmonary toxicity

There are not many pulmonary complications relating to NSAIDs, but aspirin-exacerbated respiratory disease (AERD) is probably the most common drug-related event. It presents with bronchospasm which may affect the entire respiratory tract, and is associated with other allergic symptoms, such as flushing, conjunctival injection and nasal congestion. A prior history of

asthma is not needed, and in severe form, it is very difficult to differentiate from anaphylaxis, which is also another rare and feared NSAID side-effect.

The cause of bronchospasm seems to relate to the COX-1 enzyme. Bronchospasm is very rare in patients using selective COX-2 inhibitors, even if there is a prior history of AERD.

Pulmonary infiltrates with eosinophilia is another documented reaction.

### Haematological toxicity

All three bone marrow cell lines may be affected. Although the red cells are secondary to bleeding complications and neutropenia very rarely occurs, they are affected nonetheless.

The antiplatelet effect is a major haematological NSAID consequence through impairment of the platelets' clotting ability via a reduction in TXA<sub>2</sub> through COX-1 inhibition.<sup>21</sup> The concentration of TXA<sub>2</sub> escalates in response to platelet activation, and then proceeds to stimulate increased coagulation. This effect is not seen with selective COX-2 inhibitors, and has been verified with in vitro measures following a comparison of high-dose celecoxib, i.e. 600 mg twice daily, with placebo and naproxen 500 mg twice daily. Neither placebo nor celecoxib had any effect on platelet function, but naproxen led to a significant prolongation of bleeding time and a decrease in platelet aggregation and adhesion.<sup>22</sup> NSAIDs should be avoided in individuals with coagulation defects and thrombocytopenia for this reason.

The beneficial effect that aspirin has in preventing cardiovascular thromboembolic events is undisputable, and is due to the irreversible inhibition of platelet COX, thereby reducing platelet coagulation. The Antithrombotic Trialists' Collaboration's meta-analyses of 195 randomised trials of antiplatelet therapy, principally with aspirin, using more than 135 000 high-risk patients for cardiovascular disease, significantly reduced the relative risk of subsequent vascular events (non-fatal MI, nonfatal strokes and vascular death) by approximately 22%.<sup>23</sup> As a result of this platelet interaction and consequent bleeding potential, most NSAIDs should be discontinued 3-4 days preoperatively (one week for aspirin) to allow time for the platelets to be produced without blockage of the COX enzyme.

### Central nervous system effects

Reported manifestations of central nervous system toxicity include psychosis, cognitive dysfunction, meningitis, tinnitus, dizziness and insomnia. Psychotic and cognitive dysfunction is more commonly seen in the predisposed elderly community treated with indomethacin. Symptoms completely resolve with withdrawal of this medication. Ibuprofen has been linked to causing aseptic meningitis, more commonly reported in patients with an autoimmune disease, like systemic lupus erythematosus. However, this disease itself can also predispose to meningitis.<sup>24</sup>

## Dermatological toxicity

The spectrum of skin involvement can vary from an urticarial rash to conditions as severe as toxic epidermal necrolysis and Stevens-Johnson syndrome, although the latter two are uncommon. Pseudoporphyria, i.e. skin blistering occurring on sun-exposed areas of skin, is an interesting phenomenon that is now recognised with NSAID use.

## Conclusion

Having reviewed the literature, it is difficult to determine which of the NSAIDs is the safest to use. However, it is clear that patient characteristics and medical history, in conjunction with the use of a higher dose for a prolonged duration, place individuals at greater risk of systemic complications.

When there are concerns about AERD or peptic ulcer disease, a selective COX-2 inhibitor is a safer treatment option than that of a nonselective COX inhibitor. Although gastric complications can be reduced by the concomitant use of a proton-pump inhibitor (PPI), it should be noted that chronic use of PPIs is also accompanied by numerous challenges.

Selective and nonselective COX inhibitors should be avoided, or at best used for short periods at the lowest possible effective dose, in patients with underlying atherosclerotic coronary disease.

## References

- Howard RL, Avery AJ, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol*. 2007;63(2):136-147.
- Diaz-Gonzalez F, Gonzalez-Alvaro I, Campanero MR, et al. Prevention of in vitro neutrophil-endothelial attachment through shedding of L-selectin by nonsteroidal antiinflammatory drugs. *J Clin Invest*. 1995;95(4):1756-1765.
- Amin AR, Vyas P, Attur M, et al. The mode of action of aspirin-like drugs: effect on inducible nitric oxide synthase. *Proc Nat Acad Sci USA*. 1995;92(17):7926-7930.
- Ortiz MI, Granados-Soto V, Castaneda-Hernandez G. The NO-cGMP-K<sup>+</sup> channel pathway participates in the antinociceptive effect of diclofenac, but not of indomethacin. *Pharmacol, Biochem Behav*. 2003;76(1):187-195.
- Patrignani P, Panara MR, Greco A, et al. Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. *J Pharmacol Exp Ther*. 1994;271(3):1705-1712.
- Furst DE. Are there differences among nonsteroidal antiinflammatory drugs? Comparing acetylated salicylates, nonacetylated salicylates, and nonacetylated nonsteroidal antiinflammatory drugs. *Arthritis Rheum*. 1994;37(1):1-9.
- Coxib and Traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779.
- Bavry AA, Thomas F, Allison M, et al. Nonsteroidal anti-inflammatory drugs and cardiovascular outcomes in women: results from the women's health initiative. *Circ Cardiovasc Qual Outcomes*. 2014;7(4):603-610.
- Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *JAMA*. 2015;313(8):805-814.
- Hall D, Zeitler H, Rudolph W. Counteraction of the vasodilator effects of enalapril by aspirin in severe heart failure. *J Am Coll Cardiol*. 1992;20(7):1549-1555.
- Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Medicine*. 2009;169(2):141-149.
- Schmidt M, Christiansen CF, Mehnert F, et al. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. *BMJ*. 2011;343:d3450.
- Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med*. 1991;115(10):787-796.
- Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA*. 1999;282(20):1921-1928.
- Papatheodoridis GV, Sougioultzis S, Archimandritis AJ. Effects of Helicobacter pylori and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. *Clin Gastroenterol Hepatol*. 2006;4(2):130-142.
- Laine L, Curtis SP, Langman M, et al. Lower gastrointestinal events in a double-blind trial of the cyclo-oxygenase-2 selective inhibitor etoricoxib and the traditional nonsteroidal anti-inflammatory drug diclofenac. *Gastroenterol*. 2008;135(5):1517-1525.
- Goldstein JL, Eisen GM, Lewis B, et al. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. *Clin Gastroenterol Hepatol*. 2005;3(2):133-141.
- Yared A, Kon V, Ichikawa I. Mechanism of preservation of glomerular perfusion and filtration during acute extracellular fluid volume depletion. Importance of intrarenal vasopressin-prostaglandin interaction for protecting kidneys from constrictor action of vasopressin. *J Clin Invest*. 1985;75(5):1477-1487.
- Cho E, Curhan G, Hankinson SE, et al. Prospective evaluation of analgesic use and risk of renal cell cancer. *Arch Intern Med*. 2011;171(16):1487-1493.
- Garcia Rodriguez LA, Williams R, Derby LE, et al. Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. *Arch Intern Med*. 1994;154(3):311-316.
- Patrono C. Aspirin as an antiplatelet drug. *N Eng J Med*. 1994;330(18):1287-1294.
- Leese PT, Hubbard RC, Karim A, et al. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. *J Clin Pharmacol*. 2000;40(2):124-132.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71-86.
- Rodriguez SC, Olguin AM, Miralles CP, Viladrich PF. Characteristics of meningitis caused by ibuprofen: report of 2 cases with recurrent episodes and review of the literature. *Medicine (Baltimore)*. 2006;85(4):214-220.