

# Clinical pharmacology

## Non-steroidal anti-inflammatory drug use in sports medicine

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in sports medicine to suppress inflammation and pain after soft-tissue injuries. However, the adverse consequences and the side-effects of NSAIDs are often underestimated.

### Mechanism of NSAID action

NSAIDs inhibit tissue inflammation by inhibiting cyclo-oxygenase (COX) pathway, with a reduction in the synthesis of pro-inflammatory prostaglandins. COX pathway is responsible for transforming arachidonic acid to prostaglandins, prostacyclins and thromboxanes. There are two main isoforms of the COX enzyme: COX-1 (constitutional) and COX-2 (inducible). COX-1 is found in most tissues and is responsible for cellular functions such as cytoprotection of the gastrointestinal tract, platelet aggregation and renal blood flow. COX-2 is induced during an inflammatory response and is responsible for sensitising pain receptors, elevating body temperature and recruiting inflammatory cells toward areas of tissue injury. Non-selective NSAIDs inhibit both isoforms, relieving the COX-2 induced inflammatory response, but at the expense of inhibiting the constitutional COX-1 enzyme as well. Many of the NSAID-induced side-effects are due to the inhibition of the constitutional cellular processes performed by the COX-1 enzyme. In an attempt to minimise COX-1 side-effects, selective COX-2 inhibitors were developed.

The decrease in the inflammatory response to NSAIDs may be beneficial but may also cause harm.

### Musculoskeletal side-effects

NSAIDs are frequently prescribed by practitioners and used by athletes with limited recognition of the potential musculoskeletal side-effects. There is increasing evidence that the inflammation resulting from injury is necessary for adequate tissue repair and NSAIDs may have a deleterious effect on the regeneration process. The inflammatory response is essential for the phagocytic function to clear away injured cells and to initiate a regenerative response for healing to take place.

The use of NSAIDs for muscle injuries remains controversial due to limited human data, therefore prescribing should be cautious and pathology specific. Limiting the early inflammatory response may be beneficial, but NSAID use may be detrimental in the later stages of muscle healing.

NSAIDs are useful in treating inflammatory pathologies such as tenosynovitis and soft-tissue impingement, but not conditions such as tendinopathies and fractures. Tendinopathy is in most cases degeneration, with no evidence of inflammation. Prostaglandin inhibition by NSAIDs may lead to increased leukotriene production and potential tissue damage. NSAIDs have the potential to cause tendon damage through increased leukotriene formation. Furthermore, tendinopathies have a tendency to chronicity, requiring prolonged treatment with NSAIDs and exposing users to prolonged use with NSAIDs. Increasing evidence suggests that regular use of NSAIDs may interfere with fracture healing and lack of COX-2 function seems to be the principal reason for impaired healing.

### Renal side-effects

In most circumstances, NSAIDs do not pose a significant risk to patients with normal renal function. In athletes NSAIDs may harm the kidneys by directly causing acute interstitial nephritis and indirectly by decreasing intra-renal blood flow.

Acute interstitial nephritis is an acute inflammatory condition that specifically affects the renal tubules and interstitium and occurs as a hypersensitivity reaction.

Dehydrated athletes have a decrease in effective circulating volume and diminished renal perfusion, requiring the renal system to rely on the vasodilatory effects of prostaglandins produced primarily by COX-2. NSAID use may further compromise renal blood flow by inhibiting prostaglandin-induced vasodilation and may cause ischaemic injury.

The renal effects of NSAIDs do seem to be dependent on the type of NSAID, dose and duration of treatment. Aspirin seems to be the least likely to impair renal function.

### Cardiovascular

Although the benefit of low-dose aspirin in cardiovascular disease is well established, the use of other NSAIDs may be associated

with increased cardiovascular morbidity. NSAIDs have the potential to aggravate hypertension, cardiac failure and oedema: NSAIDs inhibit prostaglandins responsible for inhibiting antidiuretic hormone and reabsorption of chloride, causing salt and water retention.

The selective COX-2 inhibitors as a class have been associated with an increase in myocardial infarction and other cardiovascular events. Prostacyclin opposes the effects of thromboxane, a thrombogenic and atherogenic eicosanoid. Selective COX-2 inhibitors inhibit prostacyclin without concomitant inhibition of platelet thromboxane, causing cardiovascular events. Cardiovascular complications are especially common in high-risk patients with evidence of atherosclerosis.

### Haematological

NSAIDs inhibit platelet function, and any effective NSAID dose is associated with an increased risk of bleeding. NSAIDs increase the risk of developing intracranial haemorrhage after minor head injury and thus careful consideration should be taken before administering NSAIDs to athletes who are engaged in contact sports or other sports that put them at major risk of traumatic injuries. When NSAIDs are combined with anticoagulants such as warfarin, an increase in INR should be anticipated with appropriate monitoring and warfarin dose adjustment.

### Gastrointestinal side-effects

NSAIDs injure the gastrointestinal tract mainly by inhibition of the gastroprotective



prostaglandin synthesis, but also by direct topical injury. NSAIDs have a local, irritant effect on the gastrointestinal mucosa through direct contact. Dyspepsia and gastrointestinal discomfort occur in at least 20% of patients taking NSAIDs but dyspeptic symptoms correlate poorly with clinically significant ulcerations. Gastrointestinal ulceration and possible bleeding or perforation are seen in 3 - 5% of NSAID users.

The risk of ulceration increases with the daily dose of NSAIDs, duration of use, patient age and co-morbidity. The 1-year risk of serious gastrointestinal bleeding from chronic NSAID use ranges from 1 in 2 100 adults younger than 45 to 1 in 110 adults older than 75 years, with the risk of death ranging between 1 in 12 353 to 1 in 647 adults respectively.

Misoprostol taken with an NSAID prevents ulcer-related bleeding complications, but is contraindicated in pregnancy and is associated with undesirable gastrointestinal intolerance. Concurrent treatment with proton pump inhibitors or histamine-2 receptor blockers also decrease endoscopically diagnosed ulcers.

Gastrointestinal NSAID-induced side-effects are due to the inhibition of the constitutional cellular processes performed by the COX-1 enzyme. Selective COX-2 inhibitors were developed in an attempt to minimise COX-1 side-effects. Disappointingly, in clinical trials, COX-2 inhibitors lowered the incidence of ulceration only, without a

clinically significant reduction in bleeding compared with NSAIDs. Also, COX-2 inhibitors are associated with an increased risk of myocardial infarction.

### Conclusion

NSAIDs have anti-inflammatory, analgesic and antipyretic properties providing symptomatic relief for many injuries and pathologies. Nevertheless, even in healthy athletes, NSAIDs may cause adverse events. Prescribers should consider whether they prescribe NSAIDs for their analgesic, anti-inflammatory or combined properties. Analgesia, such as paracetamol, should be considered when analgesia is the primary desired outcome due to its comparable analgesic efficacy with NSAIDs but more desirable side-effect profile. Both the dose and duration minimisation should be prioritised and always be combined with appropriate physical rehabilitation. Lastly, always consider the patient's individual risk before prescribing NSAIDs.

### Further reading

Mehallo CJ, Drezner JA, Bytomski JR. Practical management: nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. *Clin J Sport Med* 2006; 16(2): 170-174.

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Shoor S. Athletes, nonsteroidal anti-inflammatory drugs, coxibs, and the gastrointestinal tract. *Curr Sports Med Rep* 2002; 1(2): 107-115.

## In a nutshell

- Always weigh the possible benefit of using NSAIDs with their potential to cause serious gastrointestinal, cardiovascular and renal side-effects.
- Consider whether NSAIDs are required for their analgesic, anti-inflammatory or combined properties. Analgesia, such as paracetamol, should be considered when analgesia is the primary desired outcome.
- NSAIDs should be avoided in the dehydrated athlete.
- When NSAIDs are used, minimise the dose and duration as best as possible while controlling symptoms.

**ERIC DECLOEDT, MB ChB, BSc  
Pharmacology (Hons)**

**MARC BLOCKMAN, MB ChB, BP-  
harm, Dip Int Res Ethics, MMed (Clin  
Pharmacol)  
Department of Medicine, Division of  
Clinical Pharmacology, University of Cape  
Town**

Corresponding author: Eric Decloedt (eric.  
decloedt@uct.ac.za)