The use of nonsteroidal anti-inflammatory drugs in sports

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Abstract

Of all medication, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used in athletes. The high consumption rates seen in sporting disciplines such as soccer and endurance sports suggest that in addition to treating injuries, NSAIDs could be used in an attempt to enhance performance. There are discordant findings in human studies that probe the benefit of NSAIDs in improving the quality of muscle or as ergogenic agents. Therefore, there is a paucity of clinical evidence that demonstrates the value of the use of NSAIDs for purposes beyond pain modulation. The inhibition of NSAIDs required for normal physiological functions by NSAIDs leads to the emergence of gastrointestinal, renal and cardiovascular side effects, which consequentially could reduce the quality of life of athletes. As such, the routine recommendation for the use of NSAIDs for the acceleration of muscle healing and performance enhancement is not justified.

Keywords: nonsteroidal anti-inflammatory drugs, NSAIDs, sports medicine

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Box 1

List of abbreviations

ARF	Acute renal failure
AIN	Nephrotic syndrome with acute interstitial nephritis
CRF	Chronic renal failure
COX	Cyclooxygenase
DOMS	Delayed-onset muscle soreness
FSR	Fractional synthetic rate
GFR	Glomerular filtration rate
GI	Gastrointestinal
NSAIDs	Nonsteroidal anti-inflammatory drugs
nsNSAIDs	Non-specific nonsteroidal anti-inflammatory drugs
PG	Prostaglandin
PGE_2	Prostaglandin E_2
PPI	Proton pump inhibitor
RPN	Renal papillary necrosis

Introduction

It is well known that intensive exercise, or physical activity performed for a prolonged time leads to discomfort and pain.[1] Within various sporting disciplines, phrases such as "no pain, no gain" are commonplace in both training and competitions.[1] Exercise-induced pain negatively impacts performance,[2] and consequentially, analgesic agents are often used and even abused by athletes.[3] Of the medications used for the alleviation of exercise-induced pain, NSAIDs are the most commonly used.[4]

The NSAIDs drug class consists of a group of heterogeneous, chemically unrelated drugs with potent analgesic, antipyretic, anti-inflammatory and antithrombotic properties.[5] These drugs are used worldwide for the treatment of pain and inflammation.[6] In athletes, NSAIDs are the most commonly used drug class. Analysis of the use of medication in the Federation Internationale de Football Association (FIFA) world cups in the period extending from 2012 to 2014 showed that NSAIDs were the most prescribed drug class in soccer players, representing 36% of reported drugs.[4] A similar trend was reported for the FIFA Women's World cups in 2003 and 2007.[4] On average, 54% of male players and 50.9% of female players in the FIFA world cups used NSAIDs during the tournament.[4]

The high intake of NSAIDs is not only limited to soccer players, as high levels of intake have been reported in other sporting disciplines.[7-9] For example, during the 2000 Olympics in Sydney, one in four athletes reported using NSAIDs 72 hours before drug testing.[9] Additionally, high usage of NSAIDs has recently been demonstrated in endurance athletes both before and during events, and such usage is without professional advice.[10]

In athletes, NSAIDs are usually administered either orally, topically, intramuscularly, or even intravenously for ailments such as colds, mild pain and inflammation, fractures, to improve healing time, to reduce swelling and to decrease the time missed from competitions.[9]

The mechanism of action of NSAIDs

The effects of NSAIDs are mediated through the inhibition of COX enzymes. Both the COX-1 and COX-2 isoforms are found in the blood vessels and kidneys.[6] The COX-1 isoform is constitutively expressed and plays a role in the regulation of the synthesis of prostanoids involved in various homeostatic physiological processes.[6] In the GI mucosa, PGs play a key role in gastroprotection and maintenance of various functions of the GI tract, and PGE_2 is particularly responsible for mediating these actions.[6] Prostanoids such as PGs (E_1, E_2 and E_3), prostacyclins and thromboxanes are involved in mediating platelet aggregation.[11] Additionally, PGE_2 plays a principal role in the regulation of sodium and water retention in the kidneys.[6]

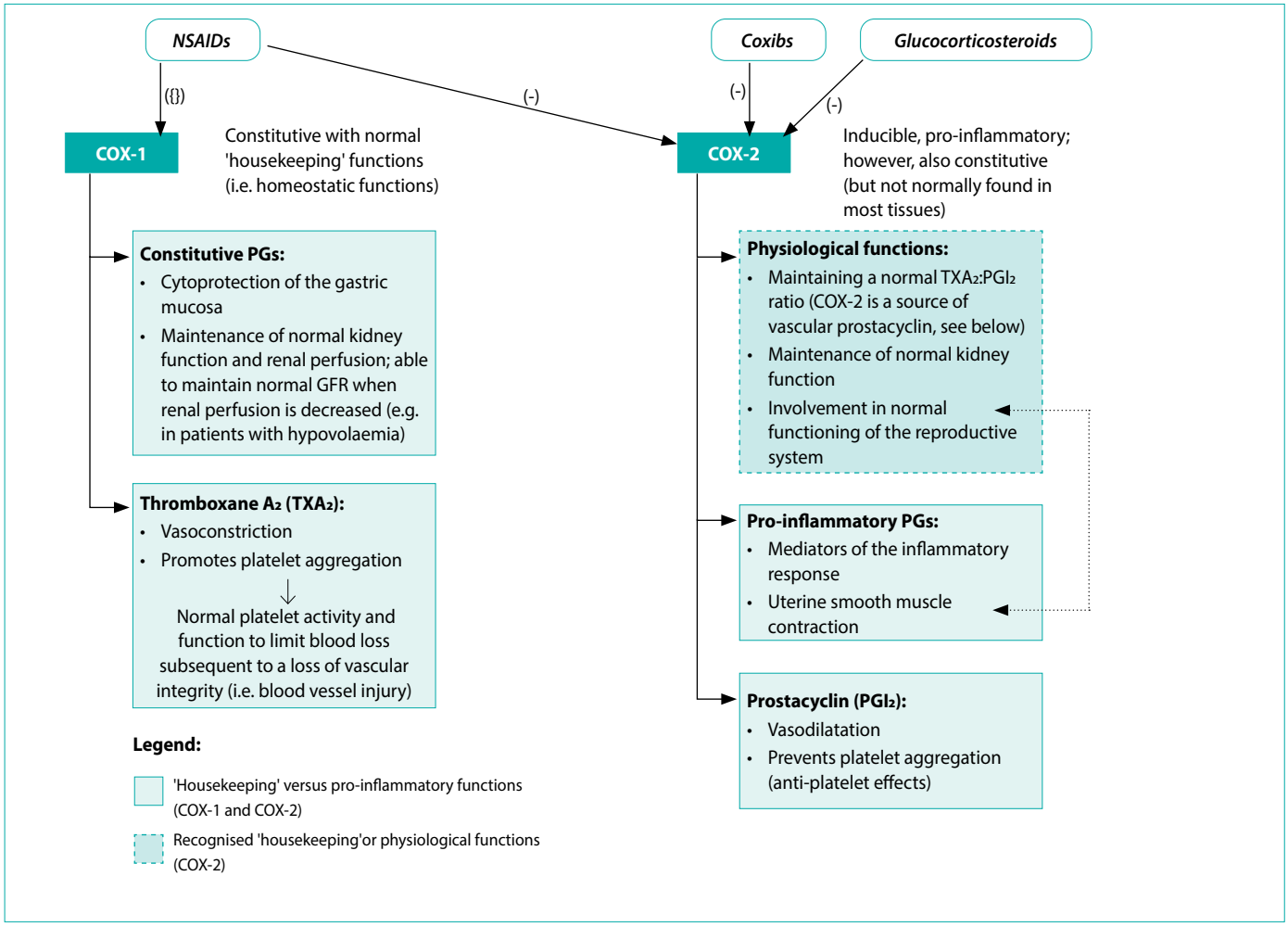

Figure 1: A comparison between the COX-1 and COX-2 isozymes[16]

The COX-2 isoform, on the other hand, is expressed in the various regions of the adult kidney and is detected upon stimulation of endothelial cells, macrophages, monocytes, and neutrophils.[6,12] Although there is a level of constitutive expression, the release of COX-2 is stimulated by pro-inflammatory cytokines, mitogens and endotoxins in inflammatory cells.[13] This isoform plays a principal role in the synthesis of PGs that mediate pain and support the inflammation process.[13] Therefore, COX inhibition using NSAIDs leads to the reduction in central and peripheral production of prostanoids, which in turn, results in an attenuated nociceptive effect and reduced inflammation.[14]

Consequentially, the alleviation of pain and inflammation at the injury site is the main goal and indication for the use of NSAIDs in sports medicine.[15] A summary of the functions of COX-1 and COX-2 is shown in Figure 1.

The effect of NSAIDs on muscle tissue

Effect of NSAIDs in treating muscle damage

Despite the popularity of NSAIDs as anti-inflammatory and analgesic drugs, evidence demonstrating the benefit of the drugs in treating exercise-induced muscle damage and DOMS remains dubious.[17]

In a study probing the effects of aspirin on female volunteers after an eccentric exercise on the elbow flexors, 650 mg of aspirin was administered to the aspirin group, 4 times a day, beginning 4 hours before exercise, continuing through to 48 hours post-exercise. Significantly less soreness was observed in the aspirin group, compared to the placebo group after 48 hours.[18]

Although many other studies have shown the benefit of NSAIDs in reducing/preventing DOMS,[19-22] many other studies have obtained contradictory findings. For example, it was shown that aspirin fails to reduce pain perception or serum creatinine kinase levels compared to the placebo.[23] In the study, 750 mg of aspirin was administered 4 times a day, 48 hours prior to an eccentric bench press and administration ended 72 hours post exercise.[23] Although there is no clear explanation regarding the disparity of these findings, different dosing regimens, degree of injury, secondary mechanisms of actions across different studies can explain the discordant observations.[24] Therefore, owing to the potential side effects caused by NSAIDs, the routine recommendation of these drugs to treat DOMS is not justified.[24]

NSAIDs and muscle protein synthesis

The maintenance of skeletal muscle tissue consists of a dynamic balance between the synthesis and degradation of muscle proteins.[25] Muscle hypertrophy occurs when the rate of protein

synthesis exceeds that of degradation.[25] After exercise, protein synthesis remarkedly increases as muscles adapt to the imposed demands.[25] Particularly, the suppression of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) has been implicated in the reduction of the synthesis rate of muscle protein.[17] Animal studies have shown that NSAIDs result in the reduction of protein metabolism.[26] Such impairment was attributed to the reduction of PG synthesis due to COX inhibition.

In human studies, there are contradictory data regarding the effect of NSAIDs on the synthesis of muscle protein. In a study conducted by Trappe et al.,[27] sedentary, recreationally active males were randomly assigned to receive 1 200 mg of ibuprofen, 4 000 mg of paracetamol, or placebo after an eccentric exercise involving the knee extensors.[27] In comparison to levels prior to exercise, the muscle FSR was significantly higher in the placebo group compared to both the ibuprofen and paracetamol group, 24 hours after exercise. Additionally, the levels of $PGF_{2\alpha}$ increased in the placebo group, while they remained unchanged in the treatment groups.[27] This led to the assumption that NSAIDs attenuate post-exercise protein synthesis through the suppression of $PGF_{2\alpha}$ production via COX inhibition.[27]

However, in subsequent studies[28-30] with a similar design, the use of NSAIDs did not reduce the FSR and protein synthesis. In one of the studies,[29] celecoxib (a COX-2 selective inhibitor) was used, and the muscle protein FSR in response to exercise was not suppressed by the drug. This led to the hypothesis that only COX-1 isoform plays a role in post-exercise muscle synthesis, while COX-2 is reactive to injury mediated stimuli.[29]

Effect of NSAIDs on satellite cells

Satellite cells are a population of stem cells resident between the basal lamina and sarcolemma of adult skeletal muscle.[31] Although these cells remain quiescent, forceful contractions, damage to the muscle, pharmacological agents, and inflammatory conditions stimulate their activation.[31] Once activated, satellite cells differentiate into myoblasts, which eventually aid in muscle tissue repair and growth.[31] There have been suggestions that NSAIDs affect the activity of satellite cells, both directly and indirectly.[32]

Various in vitro studies have demonstrated that the fusion of myoblasts is impaired when cells are treated with NSAIDs.[33-35] There are limited animal studies that probe the effect of NSAIDs on satellite cells. However, a study by Monda et al.[36] demonstrated that the activity of satellite cells is decreased in rats treated with indomethacin compared to those injected with saline.

Although it has been suggested that COX inhibition in humans using celecoxib does not affect the response of satellite cells,[37] various other studies have shown that NSAIDs result in attenuation of the cells' activity.[38-40] For example, in a study conducted by Mikkelsen et al.,[38] eight healthy males performed 200 unilateral maximal isokinetic lengthening contractions with each leg. Indomethacin (45 mg) was infused for 7.5 hours into the lateralis muscle of one leg of study volunteers, and the other leg acted as a control.[38] It was demonstrated that, while the satellite cell content doubled in non-infused muscle, there was no increase in muscle infused with the NSAID.[38]

The use of NSAIDs for performance enhancement

The negative effect of pain and exercise renders the use of analgesics for increasing the level of performance very likely.[1] The high usage of analgesics during competition compared to out-competition, administration of more multiple drugs, and the administration of analgesic agents at high doses, suggest the potential for the use of analgesic for ergogenic purposes.[1] The World Anti-Doping Agency (WADA) prohibits the use of drugs that either have the potential or enhances sport performance or represents an actual or potential health risk for athletes and violates the spirit sport described in the introduction of the WADA Code.[41] Although analgesics such as glucocorticoids are banned, NSAIDs are not prohibited despite their potential health risks because they are not considered as ergogenic agents.[41]

A recent meta-analysis highlighted the paucity of substantial evidence of the benefit of NSAIDs as performance-enhancing agents.[5] The authors analysed 13 parallel-group and 10 cross-over trials, leading to a total of 366 and 148 subjects, respectively.[5] There was no significant difference in the performance indices, perceived pain and time till exhaustion in the NSAIDs group, compared to the controls.[5] The analysed studies had limitations such as i) low doses tested, which are different from the supratherapeutic doses that athletes often use, ii) heterogeneous exercises compared to what is typically observed in the real sporting environments, and iii) low levels of evidence.[5] Therefore, the benefit of NSAIDs for performance enhancement is currently questionable. However, the absence of evidence is not evidence of the lack of the ergogenic effect,[5] some athletes may experience a benefit of NSAIDs outside doses and exercise settings that were not evaluated in the trials. It is, therefore, very imperative to consider the side effects of NSAIDs prior to the use of the drugs for such a benefit.

Side effects of NSAIDs

Despite the widespread use of NSAIDs, many of these drugs are associated with numerous side effects.[6] The protective functions of PGE_2 and prostacyclin can be reduced by the use of NSAIDs, leading to the emergence of aberrations in the function of cardiovascular, GI, and renal systems.[42]

In athletes, NSAIDs within normal or supratherapeutic doses have been shown to increase the risk of side effects such as renal dysfunction, cardiovascular events, bleeding, ulcers, kidney failure[42] and hyponatraemia during exercise.[43] Due to the inhibitory effects of NSAIDs on platelet function, the clotting mechanism can be hindered by up to 50%,[44] and this is of particular concern in contact sports or sports involving physical trauma.[1]

Additionally, the use of NSAIDs may enable athletes to resume exercise before they have fully healed, and this puts them at risk for further injury.[1]

Cardiovascular side effects

Mechanisms involved in fluid retention, heart failure and hypertension with non-selective NSAIDs and COX-2 inhibitors

In athletes and in sport this is an extremely important consideration especially in long term use. This may be due to the presence of COX-2 in the kidneys and the effect of COX-1 in maintaining a normal GFR (Figure 1). Inhibition of these enzymes by NSAIDs and selective COX-2 inhibitors will result in renal effects with different degrees of sodium and fluid retention depending on the agent.[12] PGs are synthesised in the kidneys and disruption of their synthesis by the nsNSAIDs can result in ARF, acute nephritis, electrolyte imbalances and a reduction in renal perfusion.[12,45,46] 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 that develop fluid retention will eventually develop CHF.[12,45,46]

Within the group there may be varying degrees of influence by the NSAIDs on blood pressure. Indomethacin is the most potent inhibitor of PGs and is also associated with the highest incidence of heart failure and provides great challenges in blood pressure control.[12,45,46] The NSAIDs (both non-selective and selective) antagonise most of the important agents used to manage hypertension, thus aggravating the condition.[12,45,46]

As stated above, the cardiovascular risk profile of the NSAIDs differs between the drugs, and currently, naproxen seems to be the safer choice (Figure 2), particularly when compared to diclofenac, which currently carries a warning, especially when used in patients with an existing cardiovascular risk profile (such as high blood pressure, raised blood cholesterol, diabetes or smoking).[47]

A fixed-dose combination containing 500 mg of naproxen and 20 mg of esomeprazole (Vimovo®) was introduced to the South African market towards the end of 2013.[48] This product effectively combines the nonsteroidal, anti-inflammatory action of naproxen with a PPI, so as to enable ease-of-use for patients who require NSAID therapy with the addition of an effective gastroprotective agent.[48] It is currently indicated for 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 gastro-duodenal ulceration.[48]

Naproxen is the only traditional nsNSAID that, at its full dose of 1 000 mg per day, does not exhibit an increase in cardiothrombotic risk.[49] 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).[6,50] Furthermore, with reference to its safety profile, the fixed-dose combination of naproxen/esomeprazole has shown significantly improved

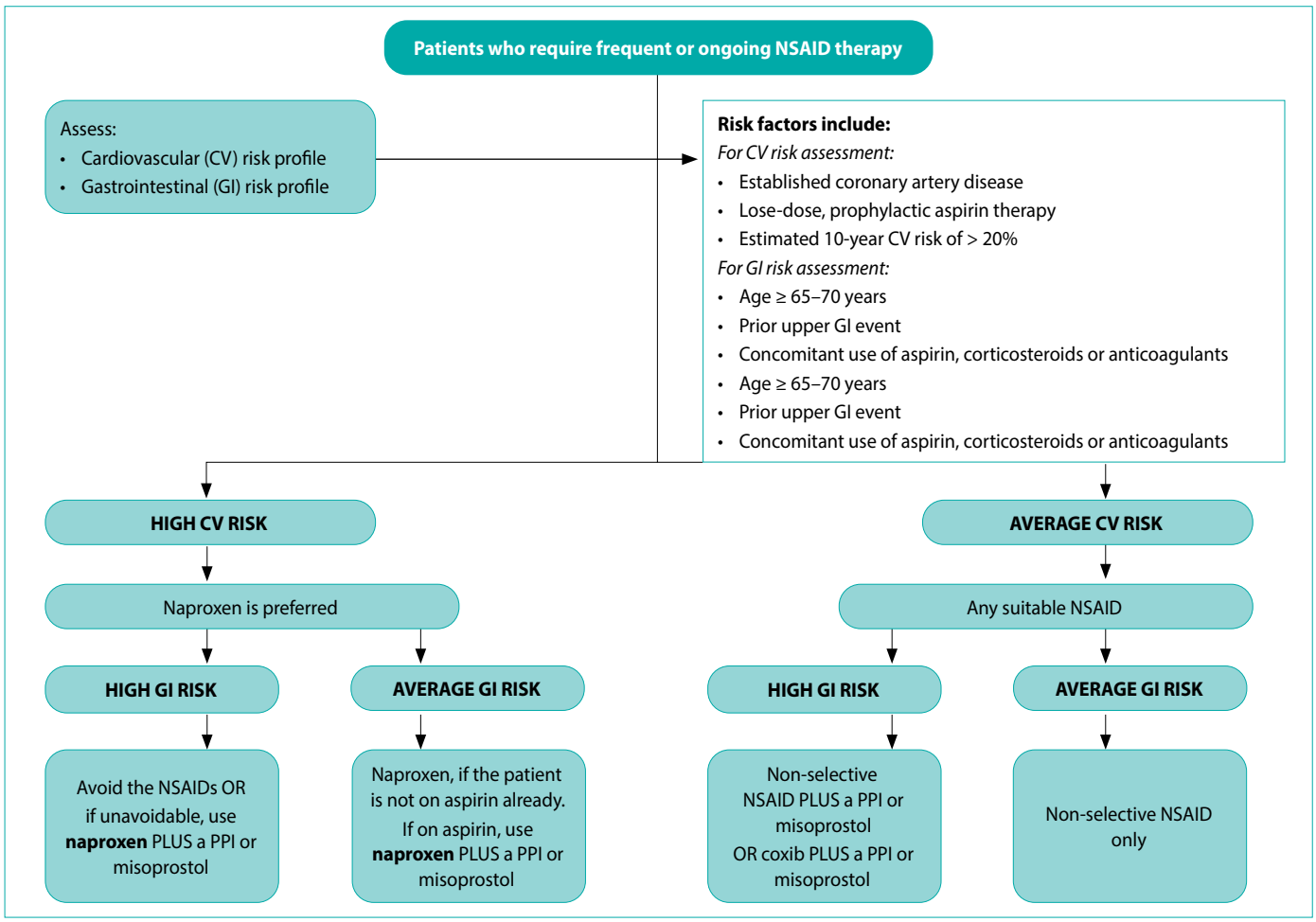

Figure 2: Management algorithm for frequent or ongoing NSAID therapy (adapted from Chan et al.)[51]
NSAID – nonsteroidal anti-inflammatory drug, coxib – cyclo-oxygenase-2 selective inhibitor, PPI – proton pump inhibitor

GI tolerability when compared to enteric-coated naproxen on its own, with significantly fewer gastric ulcers compared to the latter.[6,49]

Commonly observed adverse reactions that were reported and associated during the conduct of clinical trials with the fixed-dose combination included erosive gastritis, dyspepsia, gastritis, diarrhoea, gastric ulceration, upper abdominal pain and nausea.[6,48] It remains a recommendation, as for all NSAIDs and coxibs, that the lowest effective dosage, for the shortest possible duration, and based on the patient's individual treatment plan, should be utilised.[6,48]

Gastrointestinal effects

Pathophysiology of NSAID-induced gastric damage and other toxicities

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

- systemic inhibition of endogenous mucosal PG synthesis, and
- direct or topical irritation of the gastric epithelium.

Systemic inhibition of endogenous mucosal PG synthesis is the result of their inhibition of the COX enzyme. COX is the rate-limiting enzyme in the conversion of arachidonic acid to PGs and is inhibited by the NSAIDs. Two COX-isoforms have been identified, namely COX-1 and COX-2 (Table I).[16]

The side-effects associated with the NSAIDs are due to the non-selective inhibition of COX-1, while their anti-inflammatory properties are due to the inhibition of COX-2. Non-selective or traditional NSAIDs (e.g. NSAIDs such as 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.[52]

The addition of aspirin to a selective COX-2 regimen further reduces the benefit of the ulcer-sparing abilities and increases

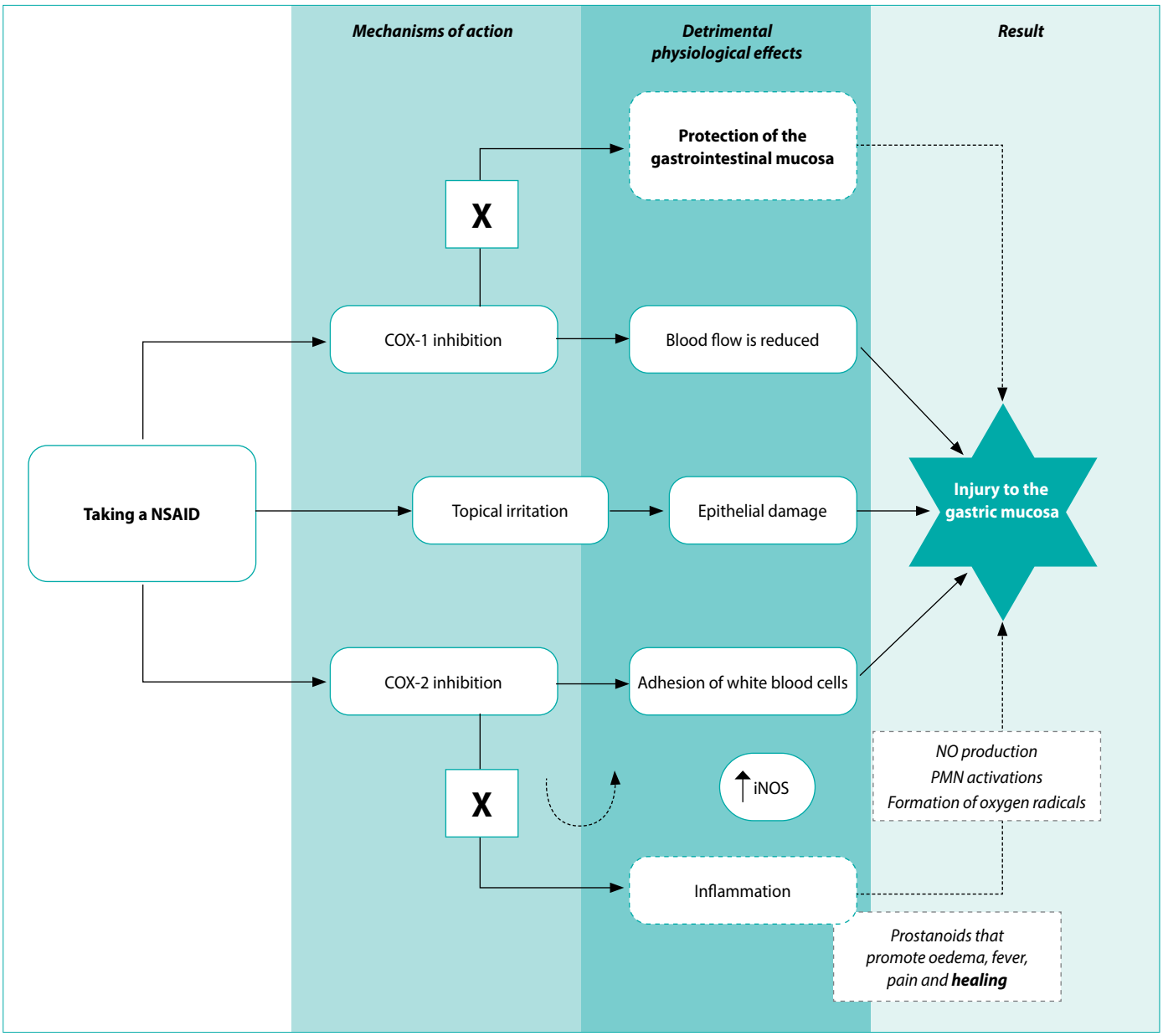

Figure 3: Pathogenesis of gastric damage induced by NSAIDs (including aspirin) (adapted from Wallace and Vong)[52]

Table I: The regulation and location of the COX isoforms

	COX-1	COX-2
Where they are normally found	Mostly found in body tissue, which includes the stomach, kidney, intestines and platelets	Undetectable in most tissues during normal physiological conditions but is particularly expressed in inflammatory conditions and arthritis
Functions	Produces protective PGs that regulate physiological processes such as: • GI mucosal integrity • Platelet homeostasis • Renal function	• Mostly induced unregulated through inflammatory stimuli such as cytokines, which then produces PGs responsible for fever and pain • Is also expressed under normal physiological circumstances in the brain, kidneys and reproductive tract

the ulcer risks.[53] The use of clopidogrel and other medicines that impair angiogenesis do not cause ulcers, but rather prevent the healing of gastric erosions that may lead to ulceration and bleeding.[53] Angiogenesis is important for the repair of GI mucosal disruptions.[54]

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 gastric ulcers were prevented.[52] However, the neutrophil adhesion in the vascular endothelium contributes to NSAID-induced gastropathy in two ways:

- physical obstruction of capillary flow, and
- release of tissue-damaging proteases and oxygen-derived free radicals once 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 PG synthesis by the mucosa. It also triggers the key event in the pathogenesis of NSAID-induced gastropathy.[52] Traditional NSAIDs vs coxibs:Celecoxib® is known to cause less harm to the GI tract because of the mechanism by which this drug selectively inhibits COX-2. Geriatric patients may still experience GI intolerance (17%), although the appearance is lower than for traditional NSAIDs (21–30%).[52]

Renal effects

The pathophysiological role of prostaglandins in the kidney

The normal function of COX-1 in the kidney is to control renal haemodynamic and GFR. The function of COX-2 affects water and salt excretion.[55] NSAIDs can cause both ARF and CRF. Various forms of decreased renal function or renal failure have been observed.[56]

A reduced glomerular filtration rate

The GFR is indicative of damage to the renal system. When a patient presents with either ARF or CRF, a reduction in the GFR will be noted.[56]

Acute renal failure

ARF is a rapid and sustained disruption of the normal kidney function that leads to an accumulation of waste products (urea and creatinine).[56] ARF as a potential side-effect of NSAID usage, is duration and dosage-dependent and is reversible.[56] The mechanism through which the NSAIDs can cause ARF is via their inhibition of the production of PGs and the resultant decrease in the blood flow to the kidneys.[6,56]

Patients with a 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 (ARBs), angiotensin-converting enzyme inhibitors (ACE inhibitors), the aminoglycosides and diuretics pose an increased risk for the development of ARF.[6,56]

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, such that hypoxia occurs in these structures. Several of the NSAIDs (including celecoxib) can cause RPN and presents with high levels of urea and creatinine in the bloodstream.[56,57]

Nephrotic syndrome with acute interstitial nephritis

NSAIDs can cause a nephrotic syndrome due to their inhibition of COX that would normally increase the production of the products of the arachidonic acid cascade.[56] Patients with nephrotic syndrome can present with oedema, proteinuria, foamy urine, oliguria, and haematuria. NSAIDs can also cause AIN due to inflammation in interstitial spaces between the kidney tubules or due to hypersensitivity reactions to these drugs. AIN is a rare disease; it is reversible, and may already be present within days after NSAID exposure.[22,56]

Chronic renal failure

The use of NSAIDs can cause CRF due to interstitial nephritis or papillary necrosis. Patients are at a much greater risk of developing CRF if they previously suffered from ARF. Any NSAID that is used on a chronic basis could potentially cause CRF in certain patients.[16]

Conclusion

In summary, despite the widespread use amongst athletes, the rationale supporting their use beyond their pain modulating and anti-inflammatory effects are not strongly supported in the literature. Although in vitro and animal studies do suggest the potential benefits of the use of NSAIDs by athletes, human studies

have discordant findings. This is mainly due to the heterogeneity of the study designs and the lack of adequate recapitulation of the real-life sporting environment within these studies. As such, the routine recommendation for the use of NSAIDs for the acceleration of muscle healing and performance enhancement is not justified. There are numerous side effects of NSAIDs, which could negatively affect the quality of life of athletes. Therefore, serious considerations should be made by athletes and medical personnel when these drugs are used in sports medicine.

Conflict of interest

The authors have no conflicts of interest to declare.

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