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Pain management in sports medicine: Use and abuse of anti-inflammatory and other agents

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Introduction

Over the last two decades, the health benefits associated with increased physical activity have been established.¹ However, with increased participation in physical activity comes a subsequent increase in sports and exercise related injury. It is estimated that there are over 4.2 million visits to the emergency rooms for sport and exercise related acute injury in the United States alone, and at least that number of visits due to chronic sport and exercise related injury.^{2,3} This article will focus on the use of pharmacological agents in the acute management of these injuries.

Use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) in sporting competition

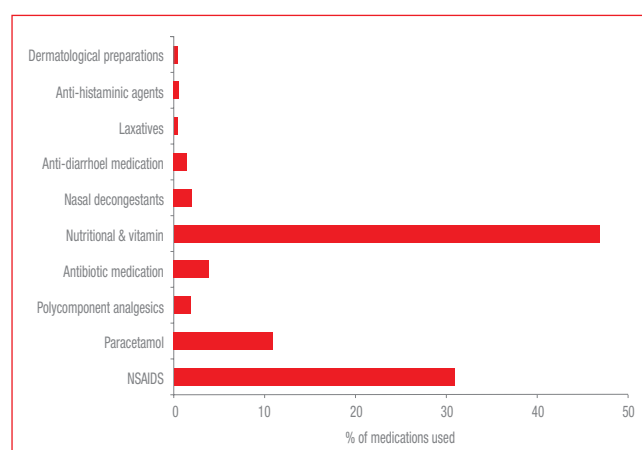
It is widely believed that use or abuse of analgesic medications and NSAIDs is widespread in sports medicine. However, the use of these agents on the African continent was previously unknown. In 1996, at the finals of the African Nations Cup Football Tournament, we undertook a study to investigate this issue. As part of the FIFA testing procedure, the team physicians of the 15 teams were asked to complete a questionnaire prior to each match. The team physicians listed the prescribed medication or supplement ingested, injected or taken per rectum for each of the 16 squad members in the 72 hr period prior to the match.

In total, 32 matches involving 544 player/match exposures occurred during the tournament. The composition of all agents used by players during the tournament is shown in Figure 1.

Thirty-one per cent of the players had injected NSAID agents in the period prior to the match. Of the NSAIDs diclofenac

was the most common (19%) followed by ibuprofen (5%), indomethacin (3%), piroxicam (3%) and acetylsalicylate (1%). In four teams, diclofenac and paracetamol were prescribed for the entire squad, twice daily, for the three day recovery period between matches. For one team, each player was administered an intramuscular diclofenac injection prior to running onto the field. In seven cases, more than one NSAID was prescribed for a player.

Figure 1: Composition of all agents used by players during the tournament



These results indicate that whilst prescribing habits vary greatly prior to competition, NSAID abuse is very common during International level football competition on the African continent. Whilst it might be argued that prescribing patterns of these agents might have changed since this study, more recent research suggests that NSAIDs use is excessive at both FIFA World Cup and Olympic level athletes.⁴⁻⁷ Indeed, our results are higher than the reported frequency (of ingestion prior to the match) of 20% reported for the FIFA 2002 and 2006 World Cup competitions.⁵ It is probable that

rates of use of these agents are even higher in recreational athletes, especially as some of these agents are available for over-the-counter purchase. It is difficult to believe that these alarmingly high frequencies of use of these agents are for therapeutic reasons and therefore, both athletes and medical staff must believe that use of these agents might extend some prophylactic benefit to the competing athlete. Furthermore, long-term use of these agents is also a concern. As these medications are not without significant side effects, improved dissemination of knowledge regarding the use of the agents as well as guidelines for their judicious use in sports medicine should be directed at team physicians, general practitioners prescribing for recreational athletes and athletes themselves. The remainder of this article will review the agents that are used for pain management in acute sports injury and suggest a rational approach to the use of these agents.

Pain

Pain is an extremely complex phenomenon. It is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Furthermore, pain is an individual, multifactorial experience influenced by culture, previous pain events, mood and ability to cope. Acute pain is defined as “pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury”.⁸ Chronic pain “commonly persists beyond the accepted time of healing of an injury and frequently there may or may not be a clearly identifiable cause”.⁸ More recently, we recognise that acute and chronic pain may represent a continuum rather than distinct entities.

Through tissue injury, phospholipids are released from the cell membrane and are converted into arachidonic acid by the enzyme phospholipase A₂. Arachidonic acid in turn is a substrate for the enzyme cyclo-oxygenase (COX) resulting in the production of various prostaglandins (PGs). This pathway and the substances that are produced are responsible for the pain and inflammation seen in sports injury. With respect to the COX enzyme, two isoforms have been established with different functions. These are COX-1 (constitutively present) and COX-2 (induced) (Table I). The older NSAIDs inhibit both isoforms of the COX enzymes, whereas COX-2 specific inhibitors inhibit only the COX-2 isoform (COXIBs), with the possibility that selective inhibition of particularly the

COX-2 isoform could reduce the side effects of NSAIDs but still maintain the efficacy of these agents.

As clinicians, we are taught to actively treat and minimise the patient’s pain and facilitate return to pre-injury level of functioning as quickly as possible, without compromising tissue healing. Indeed, many athletically inclined patients place significant pressure on their treating physician to get them “back up and running” as soon as possible. In this endeavour, we use pharmacological agents to treat the patient’s pain so that detraining may be minimised and rehabilitation can be initiated. These agents might include analgesics, topical analgesics, non-steroidal anti-inflammatory agents, topical anti-inflammatory agents and corticosteroids. These agents will be discussed in the setting of the different forms of injury and biological tissue that is injured.

Agents used to treat pain

Analgesics

Analgesics are commonly used in the first line management of acute sports injury to reduce pain. Further use of the analgesics will depend on the intensity and duration of pain. Agents in this group include acetylsalicylic acid, paracetamol, codeine and tramadol, used either as single agents or in combination.

Acetylsalicylic acid

Acetylsalicylic acid at low doses (up to 300 mg) has both an analgesic and antipyretic effect but has an anti-inflammatory effect at higher doses. However, at the higher doses, there is increased incidence of gastrointestinal side effects. As this agent inhibits platelet aggregation and may increase bleeding, it does not have a role in the management of acute sports injuries.

Paracetamol

Paracetamol has both analgesic and antipyretic effects, but does not inhibit the inflammatory response or clotting process. It is thus safe for use in acute sports injuries at up to 3–4 g/day. The incidence of adverse effects is comparable to placebo.⁹

Table I: Differences between the isoforms of the cyclo-oxygenase enzymes (COX-1 and COX-2)

COX-1 isoform	COX-2 isoform
Constitutive	Inducible
Mainly physiological effects	Release of inflammatory mediators
Sites: stomach, intestine, kidney, platelets	Sites: macrophages, synoviocytes, fibroblasts

Codeine

Codeine is a more potent analgesic from the narcotic group. It is usually used in combination with either acetylsalicylic acid or paracetamol.¹⁰ Its use is reserved for more severe pain.

Tramadol

Tramadol is also an effective analgesic from the narcotic group. It is also an effective agent in neuropathic pain.¹¹ However, a recent study has suggested that tramadol has lower efficacy and a greater incidence of adverse events compared to a COXIB in the management of chronic lower back pain.¹² Its use in sports medicine is reserved for more severe injury, when additional analgesia is required. Ongoing need for use of this agent requires reassessment of the injury.

Topical analgesics

The majority of these agents are skin counterirritants and contain a combination of substances including methyl salicylate, eucalyptus, menthol, capsicum and camphor. The active ingredients cause erythema and blood vessel dilatation and stimulate the pain and temperature receptors. These agents can be used in addition to a warm-up and can be of some benefit for minor sprains and strains.¹³ However, they should not be used on broken skin as they can cause further irritation, blistering and contact dermatitis.

NSAIDs

Perhaps the most common agents used in the practice of sports medicine today, are the non-steroidal anti-inflammatory agents. Indeed, for many clinicians these agents are the first line of use to decrease pain, swelling and the inflammatory response when treating a soft tissue injury.

One of the main functions of NSAIDs is to reduce the production of the substances that cause the inflammatory response, and therefore decrease pain, swelling, and loss of function following an acute sports injury. However, there have always been significant side effects associated with the use of NSAIDs, in particular upper gastro-intestinal side effects and renal side effects.¹⁴ NSAIDs can possibly be linked to water retention and hyponatraemia in marathoners, but further research on this area of sports medicine is warranted.

Traditional NSAIDs carry the potential for greater adverse gastrointestinal (GIT) side effects and their effects on healing of tissues remain relatively unknown. However, they are not associated with cardiovascular side effects and are effective analgesic agents.

Topical NSAIDs

A number of NSAIDs are available in different formulations including creams, ointments, sprays, gels and patches. Agents delivered in these forms include amongst others, diclofenac, flubiprofen, ketoprofen and indomethacin. A recent systematic review of randomised controlled trials concluded that topical NSAIDs are effective in relieving the pain associated with soft tissue injuries without causing serious adverse effects.¹⁵⁻¹⁹ However, NSAID patches are not effective in prophylactic use to prevent delayed onset muscle soreness (DOMS) in trained athletes.²⁰

The Cyclo-Oxygenase-2 Inhibitors (COXIBs)

These newer agents were developed to reduce the adverse GIT effects of the traditional NSAIDs. Most studies on the efficacy of these drugs show that they are effective in decreasing pain, swelling and loss of function.²¹ However, the majority of these studies have been conducted in the osteoarthritis or rheumatoid arthritis models.²¹ There are few studies on acute sports injuries. However, in some studies it has been demonstrated that the COXIBs are as effective as the older non-selective NSAIDs in the management of ankle sprains and shoulder injuries. Studies show these agents generally are effective at decreasing pain and allow a quicker return to activity and rehabilitation.^{12,22-27} However, effects of these agents on joint stability and on joint injuries other than the ankle and shoulder are unknown.

In general, the COXIBs are associated with fewer gastrointestinal and other side effects compared to the non-selective NSAIDs, and there appears to be a sparing effect on the kidneys, provided patients are not sodium depleted.¹⁵ These are advantages over the "older" drugs. There has however been some recent concern that the COXIBs may be associated with increased risk of thrombosis (by inhibiting prostacyclin), and an increased blood pressure following administration. However, the higher cardiovascular risk of the COXIBs (leading to the withdrawal of rofecoxib) compared to the non-selective NSAIDs have been seen in relation to some COXIBs but not others.²¹ The Food and Drug Administration, however, commented that the short-term use of NSAIDs and COXIBs does not appear to increase cardiovascular risk. There may also be drug interactions, such as with warfarin (rofecoxib), cytochrome p-450 inhibitors (celecoxib), and sulphur drugs (rofecoxib). These have to be taken into consideration when these drugs are prescribed.

The effects of the (non-selective) NSAIDs and COXIBs on the healing process of various musculoskeletal tissues including bone, skeletal muscle, ligament and tendon have to be considered:

1. Bone injury

Whilst the efficacy of the NSAIDs in attenuation of the formation of myositis ossificans and ectopic bone formation has been shown, the effects of these agents on the healing process and on loosening of prostheses require further studies.²⁸ NSAIDs have been widely used in the management of fracture pain, and their inhibitory effects on the bone healing process have raised concerns.²⁸⁻³⁰ Studies evaluating fracture healing in mice treated with NSAIDs or in mice lacking the COX-2 gene demonstrate that deficiency of COX-2 impairs bone healing.³¹⁻³³ Limited clinical data also support the notion that COX-2 agents delay bone healing.³⁴ However, this finding has not been replicated in all studies.³⁴ It is apparent that both the older NSAIDs and newer COXIBs negatively affect bone healing to some extent.^{34,35}

2. Skeletal muscle injury

Using different skeletal muscle injury models in animal studies, the COXIBs have shown that they impair healing and regeneration, with reduced myofibroblast proliferation and in some instances increased fibrosis.³⁶⁻³⁸ There have been limited studies on the effect of the non-selective NSAIDs and COXIBs on healing in human athletes. One study, investigating the effects of diclofenac patches following blunt trauma showed that the intervention was safe and effective in reducing pain.¹⁷ However, most of the available studies have examined the effects of these agents on delayed onset muscle soreness (DOMS) following eccentric loading exercise. The majority of these studies have failed to show any benefit of the administration of the anti-inflammatory medication with respect to induced muscle pain.^{20,39-43} Indeed, preliminary work in our laboratory has indicated that early administration of meloxicam prior to induced eccentric load damage results in higher concentrations of creatine kinase compared to administration of the agent 48 hours after muscle damage is induced. These findings suggest that early treatment with meloxicam might increase the extent of muscle damage induced by eccentric load exercise.⁴³

3. Tendon injury

Animal studies have demonstrated that ligaments from celecoxib treated rats could resist less force and were less stiff compared to ligaments from control animals.^{44,45} To date there are no studies on humans.

4. Ligament injury

The effects of the COXIBs have been investigated in animal trials using an Achilles tendon, rotator cuff, and patellar tendon injury and repair model. Whilst improved tendon

repair was reported in one study,⁴⁶ other studies reported adverse effects of both COXIBs and non-selective NSAIDs on tendon healing.^{5,6,47}

A review of the above studies certainly suggests that the anti-inflammatory agents and indeed both the non-selective NSAIDs and the COXIBs have a significant negative effect on musculoskeletal tissue healing and this finding remains a subject of much debate.^{40,48-50} This is particularly evident with respect to animal study models. Whilst animal studies are important precursors in initial evaluation of drug safety and efficacy, care should be taken in extrapolating the results in many of these laboratory based studies to the clinical setting. Further clinical trials with respect to use of these agents in the athletic population are urgently needed. In particular, the timing of administration of the agent and relative dosing (in comparison to animal models) requires further study.

Clinical recommendations for use of analgesics and anti-inflammatories in sports medicine: Current practice in Sports Medicine Practice at the Sports Science Institute of South Africa

- As is evident from the above discussion, the inflammatory process seems to be an important part of the healing process in the musculoskeletal tissue of humans. We therefore use only analgesics in the first 48 hours following injury to allow the first part of the physiological healing process to occur. Examples of agents that are used for pain management in this phase are paracetamol or paracetamol plus codeine.
- Rest, ice, compression and elevation are important elements of the patient management in the first 48 hours following injury.
- After 48 hours post-injury, if repeat assessment of the injury reveals clinical signs and symptoms of excessive inflammation (swelling and pain), we use an NSAID or COXIB for up to a limited period (five days) as these agents have been shown to reduce pain and promote function following injury.
- If the athlete has a history of gastro-intestinal side effects or other side effect following non-selective NSAID use, paracetamol should be continued or a COXIB or COXIB plus proton pump inhibitor should be considered.
- Physiotherapy, including therapeutic ultrasound, followed by rehabilitation form an essential part of treatment from 24 hours after injury.
- Generally, if the use of an NSAID, COXIB or analgesic is required for longer than a five day period, the patient should be reassessed and the diagnosis revisited.
- NSAIDs and COXIBs should not be used prophylactically

to prevent muscle soreness after exercise or to prevent pain during sport.

- There is evidence of efficacy of use of the NSAIDs in the following injuries: ligament sprains of the ankle, knee and shoulder joints; conditions where the pathological disorder is tissue entrapment or impingement of nerves and other structures due to soft tissue swelling, for example in the following conditions: carpal tunnel syndrome, Morton's neuroma, intervertebral disc prolapse, thoracic outlet syndrome, bursitis in rotator cuff disease, trochanteric bursitis and the iliotibial band friction syndrome.
- There is no role for NSAIDs in the management of the chronic degenerative tendon conditions including Achilles tendinosis, as the pathology has been shown not to be inflammatory in origin. Furthermore, there is no evidence to support the use of NSAIDs for long-term pain from sports injury without impingement.
- Many athletes with sports injury do not take sufficient time off their training to allow for complete tissue healing. They might in fact ingest these agents to facilitate early return to sport which can put them at risk of further injury. Adequate time for recovery, physiotherapy and rehabilitation should be allowed before returning to sport.

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