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REVIEW

Evidence-based prescription for cyclo-oxygenase-2 inhibitors in sports injuries

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Abstract

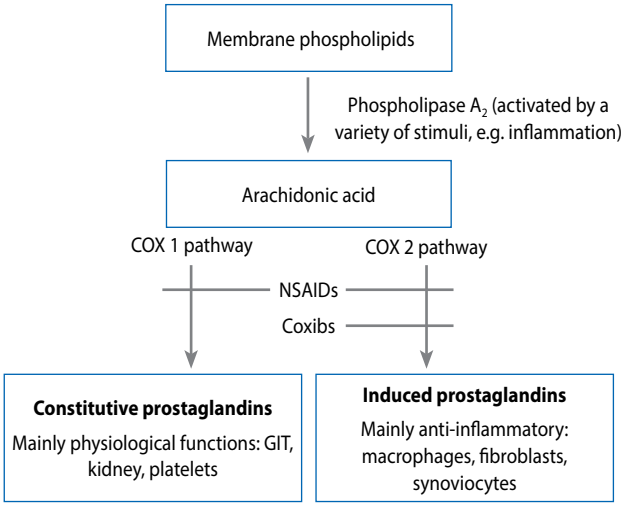
Healthcare professionals are increasingly under pressure to return athletes to play in the shortest possible time. There is limited choice in providing treatment that speeds up tissue repair, while simultaneously maintaining good quality of healing. Inflammation forms a fundamental part in the process of tissue repair. However, excessive inflammation may cause more pain, and limit functional restoration. Although the use of anti-inflammatory treatment in the form of a cyclo-oxygenase-2 inhibitor (coxibs) has been widely recognised as being effective, the potential detrimental effect on tissue repair, as described mainly in animal model studies, needs to be taken into account. The side-effects profile on the gastrointestinal tract favour coxibs over non-traditional NSAIDs. The possible effects on the renal and cardiovascular systems also need to be considered. The prescription of coxibs should be pathology and situation specific. There are no clear guidelines on the correct time of administration and the duration of the course, but it seems that the literature is in agreement that they should be administered for a limited time at the lowest effective dose possible.

Keywords: cyclo-oxygenase-2 inhibitors (coxibs), sports injuries**,** treatment

Introduction

The health benefits associated with exercise are well established. Unfortunately, the risk of an injury is inherent in exercise training.[1] According to the USA Consumer Product Safety Commission's National Electronic Injury Surveillance System, more than 1.9 million individuals had a sports-related injury that was treated in emergency departments in 2012, while a national survey in 2011 in the Netherlands revealed that there were 3.5 million new sports injuries per annum.[2,3] Overuse injuries have been reported to constitute 50-60% of all sports injuries.[4]

Pressure is mounting on healthcare professional to return athletes to play in the shortest time possible. However, limited treatments are available that can accelerate tissue repair, without affecting the quality of healing.[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat musculoskeletal pain and inflammation. Drugs in this group include acetylsalicylic acid; the traditional NSAIDs, e.g. ibuprofen, diclofenac, indomethacin and naproxen; and the cyclo-oxygenase-2 inhibitors (coxibs), e.g. celecoxib and etoricoxib. Although these drugs vary in the pathways targeted and the mechanism of action (Figure 1),[1,6] their common goal is to limit inflammation. The process of inflammation forms a pivotal role in tissue repair. However, excessive inflammation is painful, causes fibrosis and limits functional restoration.[7] Therefore, the time of administration, the dosage prescribed and the duration of anti-inflammatory treatment is important,[8] but clear guidelines are not available in the literature.



coxibs: cyclo-oxygensase-2 inhibitors, NSAIDs: nonsteroidal anti-inflammatory drugs
Figure 1: Mechanism of action

Effect on different tissues implied in sports injuries

Coxibs have become more popular than traditional NSAIDs, owing to a better gastrointestinal tract side-effect profile, but may have an effect on different tissues implied in sports injuries.[1,6,8-10] Recent research, mainly on animal models, has shown some detrimental effects on tissue repair.[11-17]

Muscle

Injured muscle heals by a three-phase process of destruction, repair and remodelling. Reducing the destruction phase allows for faster pain relief and healing. Although anti-inflammatory treatment may limit this phase, it can also limit the repair and remodelling phase.[18]

Tendons

It is now more clearly understood that tendon injury is generally not an inflammatory process,[19] but rather comprises histological changes that include hypercellularity, neovascularisation, fibre thinning and disorientation. Thus, coxibs are not indicated for their anti-inflammatory actions in degenerative tendon injury.[9,10]

Bone

A bone injury leads to a series of events, including haematoma formation, a subsequent inflammatory response and the development of granulation tissue with neovascularisation, callus formation, bone deposition and remodelling.[20] New bone, identical to previous bone, is formed. Prostaglandins play an important role in osteogenesis. Therefore, blocking prostaglandins may impair bone healing.[10] Most studies that have evaluated the effect of coxibs on osteogenesis have shown a detrimental effect on bone healing,[21-23] especially when used over a longer period, ie. from 3-12 weeks. Other studies have failed to prove this.[24,25]

Ligaments

The healing process of ligaments is similar to that in a muscle injury.[10] Improved pain levels and return-to-play time had been demonstrated in human studies in which anti-inflammatory treatment after ankle sprains was used.[26-30] The decision as to when to commence treatment post-injury is still being debated, and the effect on long-term ligament repair after the early use of anti-inflammatory treatment remains unclear.

Unfortunately, most research is on animals, and although such surveys are important precursors to clinical studies, they do not always accurately represent clinical use and efficacy in humans.[31] Coxibs have an altered metabolism across different species, and this may limit the translation of findings in animal studies to the clinical setting.[32,33] Further randomised controlled trials are needed to establish the potential negative effect of coxibs on clinical tissue-level repair.[1]

Systemic adverse effects associated with cyclo-oxygenase inhibitor use

While effective for pain relief and a reduction in inflammation, the side-effect profile of coxibs needs to be considered before they are prescribed to athletes. Celecoxib was generally well tolerated at doses of 100 mg/day, 200 mg/day and 400 mg/day, in pre-marketing studies. Adverse events were reported in 5% of treated patients, and included headaches (15.8%), dyspepsia (8.8%), upper respiratory tract infection (8.1%), diarrhoea (5.6%) and sinusitis (5%).[34,35]

Gastrointestinal tract

Coxibs were developed to selectively block the induced prostaglandin pathway, i.e. pain and inflammation.[10,36] However, there is still potential for effects like peptic ulceration, nausea, dyspepsia, constipation, erosion, perforation and bleeding, since cyclo-oxygenase-2 (COX-2) selectivity is not complete.[10,37-40] Various literature, including a meta-analysis and systematic review, has shown a reduced incidence of gastrointestinal tract side-effects with the use of coxibs, compared to that of traditional NSAIDs.[41,42]

Renal

Although coxibs are not deemed to influence normal renal physiology, a recent study demonstrated an increased risk of hyponatraemia in endurance athletes owing to impaired free water clearance.[43] Inexperience, a slow running pace, being of the female sex and the high availability of liquid on the course are factors that may contribute to hyponatremia in long-distance events.[44]

Cardiovascular

Coxibs have been associated with an increase in cardiovascular events.[45,46] FitzGerald proposed a possible mechanism that relates to the different metabolites generated by the cyclo-oxygenase-1 (COX-1) and COX-2 pathway.[47] Thromboxane (TxA_2) is generated in platelets via the COX-1 pathway, and is responsible for platelet activation, smooth muscle proliferation and vasoconstriction.[48] Prostacyclin (PGI_2) is generated in the vascular endothelial cells via the COX-2 pathway, and leads to the inhibition of platelet aggregation and vasodilation.[49,50] Selectively blocking the COX-2 pathway, as is the case with coxibs, results in TxA_2 being unopposed, and as such, the antiatherothrombotic effects of PGI_2 are removed. This postulated mechanism implies a class phenomenon, rather than a specific drug effect, e.g. rofecoxib in the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.[51] However, pharmacodynamics and pharmacokinetic profiles also have to be considered since studies on celecoxib have shown equivalent risk in non-NSAID users in developing congestive heart failure and acute myocardial infarction.[52,53] Some studies suggest that the risk increases with higher dosages of celecoxib.[45,54]

Recommendations for use in sports injuries

The ability of coxibs to decrease pain, swelling and loss of function is well documented in the literature.[55]

The efficacy of coxibs, compared to that of NSAIDs, has been reported in patients with ankle sprains,[26-30] lower back pain[56] and acute shoulder pain.[57,58]

Although coxibs seem to have a negative effect on tissue healing, most of the studies were performed on animal models.[11-17] For now, this remains a subject for debate.[59]

The prescription of coxibs should be pathology and situation specific. If analgesic treatment is the primary aim, a NSAID might not be the best choice, and a pure analgesic drug should be considered.[60] If the clinical examination reveals excessive inflammation, a coxib may be administered for a limited period at the lowest effective dose.[6,8,10] Bursitis, synovitis and nerve impingement, due to soft tissue proliferation, are conditions that respond best to anti-inflammatory treatment.[61]

Basic principles like POLICE (protection, optimal loading, ice, compression and elevation)[62] and other nonpharmaceutical modalities, e.g. physiotherapy modalities, should be introduced

in the treatment plan in order to minimise dependence on medication and expedite return to play.[6,8]

Currently, there is no rationale for the prophylactic use of NSAIDs to prevent pain during sport participation or to prevent sore muscles after exercise.[1,63] The regular intake of these drugs before exercise may lead to reduced tissue adaptation and delayed healing of musculoskeletal injuries.[64-66]

Adequate time for recovery is of the utmost importance.

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