COX-2 inhibitors

COX-2 inhibitors in sports medicine: utility and controversy

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Short term use of COX-2 inhibitors for pain management is recommended

There are approximately 4.2 million visits annually to emergency rooms for non-fatal sports and recreation related injuries in the US.¹ Sports injury leads to the release of phospholipids from cell membranes, which are converted into arachidonic acid by the action of phospholipase A₂. Arachidonic acid in turn acts as a substrate for cyclo-oxygenase (COX) resulting in the production of various prostaglandins (PGs). There are two forms of COX: COX-1 (constitutively present) and COX-2 (induced). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both types of COX enzymes, whereas COX-2-specific inhibitors inhibit only the COX-2 enzyme. COX-2 inhibitors were developed with the aim of reducing the incidence of serious adverse gastrointestinal effects associated with the administration of traditional NSAIDs. The assumption was that gastrointestinal side effects were COX-1-mediated. There are two major reasons for the use of NSAIDs and COX-2 inhibitors in the treatment of athletic injuries: to decrease excessive inflammation so as to increase the rate of healing, and to decrease pain associated with inflammation.

Among the PGs, PGE₂ is the predominant mediator of both peripheral and central pain sensitisation.² As the prostanoïd most associated with inflammatory response, the formation of PGE₂ at an injured site is an indication of peripheral inflammation. Recently, peripheral inflammation has also been shown to induce a widespread increase in COX-2³ and PGs in the central nervous system (CNS). The proinflammatory cytokine interleukins 6 and 8 are upregulated in the CNS and play a role in inducing central PGE₂ upregulation after inflammation induced by surgical trauma.⁴

There appear to be two forms of input from peripheral inflamed tissue to the CNS. The first is mediated by electrical activity in sensitised nerve fibres, and the second is a humoral signal. Both originate from inflamed tissue and produce a widespread induction of

COX-2 in the CNS. The second input is not affected by regional anaesthesia and is blocked only by centrally acting COX-2 inhibitors. Therefore, the permeability of the blood-brain barrier to currently used NSAIDs and COX-2 inhibitors becomes important.⁵ Inhibitors of COX-2 that better penetrate the blood-brain barrier may represent more efficient pain killers.⁶ They could also act to reduce many of the more diffuse aspects of inflammatory pain, such as generalised aches and pains, depression and loss of appetite, which are key aspects in determining the "quality of life" response to treatment.⁷

Exercise-induced muscle injury (EIMI) is one of the most common types of trauma associated with physical activity. An inflammatory response occurs at the site of muscle injury, and administration of COX-2 inhibitors may be beneficial for short term recovery of muscle function and reduced soreness after exercise in healthy adults. The prophylactic use of COX-2 inhibitors before EIMI remains controversial. The most common sports-related injury of the knee is anterior cruciate ligament (ACL) tear, for which surgery is a common treatment option. Pain management after ACL repair is of paramount importance for good functional outcome. Preoperative dosing of COX-2 inhibitors for ACL repair has been associated with a decrease in postoperative pain, opioid use, nausea and vomiting, recovery room length of stay, and unplanned admission to the hospital.⁸ In addition to providing short-term analgesic benefits, the use of pre-emptive multimodal analgesia including COX-2 inhibitors resulted in a significant reduction in long-term patellofemoral complications after ACL surgery.⁹ These included a reduction in the incidence of anterior knee pain, scar tissue, flexion contracture and complex regional pain syndrome. Further, patients receiving perioperative COX-2 inhibitors were more likely to return to their pre-injury level of activity including full sports participation.⁹ Sports-related injuries at a young age are a

major cause of arthritis in patients <40 years of age. Trials of COX-2 inhibitors used before surgery and for 2 weeks after in patients undergoing joint replacement surgery¹⁰ have shown improved clinical outcomes. Furthermore, early and aggressive sustained treatment with COX-2 inhibitors may ameliorate the longer lasting elements of postoperative pain, and prevent the transformation of acute into chronic pain.¹¹

Several controversial issues exist with regard to the routine administration of COX-2 inhibitors. These include a possible deleterious effect on fracture and tendon healing, cardiovascular and renal effects. Recent guidelines for acute pain management state that "multimodal analgesia improves postoperative pain control and reduces analgesia-related adverse effects". However, routine perioperative use of NSAIDs may predispose patients to an increased risk of bleeding. In contrast, COX-2 inhibitors can be administered pre-emptively to surgical patients without the added risk of increased perioperative bleeding.⁸⁻¹¹

Bone fractures are a known risk of athletic participation and can result in significant lost playing time. A variety of drugs have been investigated in animals for their effects on fracture healing. A concern regarding the perioperative use of COX-2 inhibitors is the possible deleterious effect on osteogenesis. PGs have been known for many years to have potent effects on bone metabolism, including both osteoblastic and osteoclastic activity, as well as being essential in bone repair. In these studies, COX-2 inhibitors were administered over several weeks to months at doses greater than those approved for acute pain.¹² Recently, it has been suggested that the deleterious effects of COX-2 inhibitors on fracture healing may be avoidable with short-term treatment.¹³ Furthermore, in tendon remodelling after a sport-related injury, COX-2 inhibitors may be of value in combating the negative influence associated with inflammation.

A more recent concern about the perioperative administration of COX-2 inhibitors for short term use is their possible role in increasing cardiovascular morbidity. There was a fivefold increase in the incidence of myocardial infarction in the Vioxx Gastrointestinal Outcome Research (VIGOR) study, which used 50 mg rofecoxib daily for a median of 9 months in patients with a high risk of rheumatoid arthritis, in whom the use of aspirin was precluded.¹⁴ Rofecoxib was withdrawn from the worldwide market after the interim results from the Adenomatous Polyp Prevention on Vioxx (APPROVe)

study had been examined. This long-term study was designed to investigate the effects of 3 years of treatment with 25 mg rofecoxib daily on the risk of recurrent neoplastic polyps. A 1.7-fold increased risk of myocardial infarction with rofecoxib compared with placebo was observed after 18 months of treatment. During the first 18 months, the event rates were similar in the two groups.¹⁵ The Adenoma Prevention with Celecoxib (APC) trial examined the efficacy of celecoxib for the prevention of colorectal adenoma. Celecoxib used for 33 months was associated with a dose-related 2–3-fold increase in cardiovascular events compared with placebo.¹⁶ Similar to the VIGOR and APPROVe studies, the increased risk did not become apparent until after 12 months of treatment. The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) found no increased cardiovascular risk with 200 mg celecoxib daily but a statistically significant increase in cardiovascular risk with naproxen.¹⁷ This study is of substantial clinical importance as previous prospective, long term COX-2 inhibitor studies used placebo for comparison, whereas this was the first trial to use a non-specific NSAID as a comparator drug.

The question currently facing clinicians is whether the increased cardiac risk associated with COX-2 inhibition is unique to this subclass of drugs or whether it is characteristic of all NSAIDs. The FDA reaffirmed that COX-2 inhibitors are important treatment options for pain management and that the preponderance of data show that the cardiovascular risk associated with celecoxib is similar to that associated with commonly used older non-specific NSAIDs.¹⁸ The rationale behind

this conclusion is that COX-2 inhibitors collectively increase cardiovascular risk when compared with placebo but not when compared with non-selective NSAIDs. The FDA commented that short-term use of NSAIDs and COX-2 inhibitors does not appear to increase cardiovascular risk. Practicing clinicians should assimilate these conclusions when performing a risk-benefit assessment of the value of COX-2 inhibitors for short-term use in sports related injuries.

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