

Anti-inflammatory Drugs – Their Role In Sports Medicine:

A personal viewpoint

By Chris Milne

Last year at the SMA conference in Adelaide I ran a workshop on the topic of NSAID and cox-2 agents in musculoskeletal injury. The session was well received and engendered a good level of debate and I was asked to repeat it again this year. Unfortunately, I cannot be at the SMA conference on Hamilton Island and thought that this article would give wider exposure to this important topic.

As readers will be aware, anti-inflammatory agents have been in widespread use for a variety of conditions since the development of aspirin in 1899. There are four common clinical indications for use of these agents.

1. Inflammatory arthropathies, including rheumatoid arthritis plus the seronegative arthropathies and crystal arthropathies.
2. Osteoarthritis, which is more than just a simple wear and tear disorder. Modern day thinking is that it is a pan-articular inflammatory process and, therefore, the use of NSAIDs is entirely rational for osteoarthritis. Moreover, our patients tell us that they are more effective than paracetamol despite what the published data would tend to suggest.
3. Soft tissue injuries with a significant inflammatory component. This includes an effusion in a joint following an injury or inflammatory conditions involving muscle or tendon attachments.
4. Anti-inflammatory agents are effective analgesics in their own right and have been particularly useful for post-operative and dental pain and headache.

Their mechanism of action has only been understood following the discovery of prostaglandins in the 1960s. The NSAIDs inhibit prostaglandin synthesis. They also inhibit leukotriene synthesis,

lysozyme release and neutrophil aggregation. At the cell membrane level, they alter ion fluxes.

The major publicity in the last decade or two has been around their toxicity; their efficacy is unquestioned. A lot of the research effort has gone into making agents that are less toxic to the upper GI tract. This is because dyspepsia on standard NSAID affects about 10 per cent of people taking these drugs. However, the vast majority of people with dyspepsia do not have any serious medical consequence of this. There is a small minority of patients, often with coexistent disease or who have had a previous GI bleed or are taking corticosteroids, particularly those over the age of 60, who can have more serious GI bleeding and this can be fatal in some circumstances.

Therefore, a lot of effort has gone into developing more "GI friendly" NSAIDs. These agents selectively inhibit the cox-2 enzyme which affects chondrocytes and synovium, whilst sparing the cox-1, or "housekeeper", enzyme which maintains the mucous lining of the stomach, among other things. However, like selectivity for beta blockers, cox-2 selectivity is only a relative phenomenon.

Importantly, cox-2 agents are no more effective than traditional agents and their only advantage is that they are better tolerated by the majority of people who experience dyspepsia on a traditional NSAID. However, there is a small minority of people who experience dyspepsia even on cox-2 agents.

An additional feature of concern was the widely publicised data with regard to Vioxx (rofecoxib) which, when used by doctors in the USA at a dose of 50mg daily, was found to have over twice the risk of adverse vascular events. The actual odds ratio was 2.19. However, in the dosage used widely in Australasia, i.e. 25mg per day, the odds ratio was

only 1.33. It will be no surprise to hear that those at greatest risk of vascular events were older people with adverse vascular risk factors.

All of this publicity has led to a lot of scaremongering, in my view. Patients have been paranoid about the use of these drugs and doctors have become pretty reticent about prescribing them.

What is the actual truth of the matter?

The largest meta-analysis of 138 randomised control trials involving 145,373 people found that the absolute risk of cardiovascular events, mainly myocardial infarction, increased from 0.9% per year to 1.2% per year across patient populations. This is a risk that most people would not worry unduly about. However, the media reported that the relative risk increased by 42%, which is correct but gives ample opportunity for scaremongering. This data was published in the British Medical Journal in 2006.

Since then there have been other side effects reported regarding other cox-2 agents. In particular, Vextra (valdecoxib) was found to have adverse skin reactions. More recently, Prexige (lumiracoxib) was found to have adverse effects on the liver. Both of these side effects were pretty uncommon but the regulatory authorities, in my view, were overly cautious and withdrew both of these agents from the market, thus denying clinicians the opportunity to use them in patients who may have gained from their use, and in which other agents had been tried and found to be unacceptable.

All of this has led to a situation where clinicians often feel on the defensive with regard to use of NSAIDs. As we all know, time is a commodity which is in short supply and rather than detail the pros and cons of a particular situation,

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Which sports medicine conditions are NSAIDs and cortisone injections useful for?

By John Orchard

One simple way to think about NSAIDs and cortisone – which can help best identify the conditions where they are useful – is that they are tissue “shrinkers”. By inhibiting inflammation, they also suppress the remodelling part process involved in turning over new tissue. Both NSAIDs and cortisone therefore have catabolic (the opposite of anabolic) properties. The question to ask yourself when considering treatment with cortisone and NSAIDs for musculoskeletal conditions is: “do I really want to shrink tissue?” If the answer is yes, then these forms of therapy are probably the best option. If the answer is no, then traditional analgesics may be a better choice for pain relief.

Which musculoskeletal conditions are ideal for using NSAIDs and cortisone injections? For any process that involves nerve impingement they will be first line therapy. The soft tissues (or even bone) causing the impingement may be “shrunk” slightly by the anti-inflammatory effect, but nerve, being a very low turnover tissue, won’t be directly affected by the anti-inflammatory action. The result is reduced pressure on the nerve and, hopefully, better pain relief than you might expect with a pure analgesic. Impingement conditions not involving nerves can also show great improvement with anti-inflammatory treatment – shoulder and ankle impingements, in particular, and conditions like iliotibial band friction syndrome of the knee. Conditions with ectopic tissue like myositis ossificans (where calcium deposits are laid down in muscle following a ‘cork’) also respond well to anti-inflammatory treatment, used to ‘shrink’ the offending new tissue. True ‘bursitis’, like those seen in prepatellar and olecranon bursas, is

still a great indication for a cortisone injection or NSAID treatment (in superficial cases like these, gel may even be preferable to tablets).

Where should NSAIDs and cortisone injections be avoided? For degenerative conditions which involve delayed repair of an important tissue, cortisone injections and even NSAIDs can be detrimental. Pure tendinopathies, particularly for heavy load-bearing tendons like the Achilles, are a prime example where the risks and detrimental effects of anti-inflammatory medications may outweigh the benefits. Even in fractures, animal (and some human) studies strongly suggest that repair will generally be delayed by NSAID use. Therefore, in acute injuries where an important tissue is damaged, use analgesics in preference to NSAIDs. Similarly, in chronic degenerative (as opposed to inflammatory) arthritis, cortisone injections may lead to longer-term harm even after good short-term pain relief. For smaller joints like the A/C joint or finger joints, the effect of a cortisone injection in relieving scar tissue may outweigh any damage to the articular cartilage, but equation may swing around for an important large joint like the knee.

The extreme examples are easy to advise on. The difficult or ‘grey’ zone is when you have two competing processes which mean the effect of anti-inflammatory treatment could go either way. A classic is in shoulder pain – a cortisone injection might help relieve impingement, but if there is a rotator cuff tendon tear associated, it may also reduce healing and lead to extension of the tear. This is where investigation may be helpful in the decision on using

an injection. If an ultrasound shows an intact rotator cuff, it is a green light for a cortisone injection into the subacromial space. Degenerative tendinopathy may be an amber light with respect to an injection and a full-thickness tear may be a red light.

Imaging may be helpful for determining which muscle strains might be best treated with NSAIDs. A hamstring tear proven on MRI scan may have its healing potentially delayed by NSAIDs and lead to a greater risk of recurrence (http://www.richmondphysiotherapyclinic.com.au/hamstring_muscle_strain.pdf) whereas a back-related hamstring may benefit and have quicker return to play using NSAIDs.

It goes without saying that there are many areas of the body where it is important to make a correct diagnosis before automatically reaching for NSAIDs. Forefoot pain, for example, might be caused by a metatarsal stress fracture or Morton’s neuroma. Stress fracture healing would probably be decreased by the use of NSAIDs or cortisone, whereas Morton’s neuroma might respond very well and be improved with their use.

Even for areas where you should be cautious with cortisone injections, there may sometimes be good results. An excellent Australian study published in the BMJ in 2006 shows that cortisone injections are helpful for tennis elbow (which is a tendinopathy) in the short-term, but detrimental in the longer term. Reading this study makes you think twice about using cortisone in this condition, although there will be circumstances where short-term improvement can be very important to the patient whose long-term prognosis

the line of least resistance is just to move on and use some agent whose role is less controversial but which may, in itself, have lower efficacy.

Ultimately, the experience of the last five years is likely to lead to a lower rate of investment in potentially innovative medicines in future and, thereby, a lessening of the choice of medicines available to clinicians and patients.

What is a logical way through all of this?

1. I would advise clinicians to assess the severity of the pain, i.e. mild, moderate or severe.
2. They should ask about previous adverse drug reactions and relevant medical history. Such reactions include:
 - a. Dyspepsia (burning abdominal pain) with aspirin or other NSAIDs.
 - b. Reduced blood flow to kidneys can occur on NSAIDs. Usually this is occult but it may present as fluid retention in older people or those with borderline cardiac function.
 - c. A flare of asthma with NSAIDs is rare but well publicised and, once again, can put people off using

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is good anyway. A high demand patient (ranging from a high level tennis player to a car mechanic who gets tennis elbow pain from work) is the type scenario to be wary of injections. This sort of patient will still want to be loading the elbow in 6 months time and won't appreciate it if the cortisone "wears off".

There are some patients who will swear by cortisone injections and NSAIDs for many conditions and others who claim to get no effect even for conditions where they aren't meant to be as useful. This is part of the unknown zone in medicine. Maybe certain patients have over-active repair systems which regularly lay down excessive scar tissue. These patients may do well with cortisone injections and NSAIDs for many conditions. Knee medial ligament tears are one of many conditions in the body that can alternately heal badly by being "too loose" or "too scarred". For the patient that is not laying down much scar tissue and has a medial ligament that is not tightening up sufficiently, avoid using NSAIDs and cortisone.

these agents in all asthmatics which, I believe, is irrational. However, such a flare may be serious so it needs to be looked out for.

In summary, most athletes can take standard NSAIDs without getting dyspepsia. For those who cannot, there are three options:

- a. Use of paracetamol 500mg two tablets up to four times daily is the option that no authorities would dispute. This agent is not associated with any adverse GI effects unless taken in overdose, where it can have toxic effects on the liver.
- b. Use of a standard NSAID with a low GI toxicity profile, e.g. Ibuprofen under cover of Losec (omeprazole).
- c. Use of a cox-2, e.g. Celebrex (celecoxib) or Arcoxia (etoricoxib), however it needs to be understood that these agents are more expensive. In the short term, e.g. one week for settling a joint effusion, this is not a major consideration provided it is pointed out to the patient prior to them leaving the doctor's office.

Finally, empowerment of patients involves giving them a choice and providing them with an information sheet detailing at least some of the information listed above. By this means, the clinician can be assured that the patients have access to relevant background material and are not denied use of medicine that could be of significant benefit to them.

It needs to be understood that the above is a personal viewpoint but, nevertheless, one that is shared by a large number (I might even say the majority) of clinicians who are well informed about the use of these agents.

References:

1. Practical Management: Nonsteroidal Antiinflammatory Drug (NSAIDs) Use in Athletic Injuries
Mehollo CJ, Drezner JA, Bytomski JR
Clin J Sport Med 2006; 16 : 170-174
2. Cyclo-Oxygenase-2 Inhibitors: Beneficial or Detrimental for Athletes with Acute Musculoskeletal Injuries
Warden SJ
Sports Med 2005; 35 : 271-283

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Alternatively, for the patient that has a solid medial ligament but is getting a lot of pain at the insertion (perhaps developing a Pellegrini-Stieda lesion) then NSAIDs and cortisone would be beneficial.

It is also worth remembering the systemic side effects of NSAIDs in particular. They increase the risk of gastric bleeding, increase blood pressure and can be harmful for patients with poor kidney function. The upside is that they reduce the risk of bowel cancer and reduce clotting. These factors can help decide which patients should avoid (or may benefit from) NSAIDs. Cox-2 specific NSAIDs in general are better for stomach and worse for heart.

Even though NSAIDs and cortisone are out of favour for certain conditions, like tendinopathies and osteoarthritis, it is fortunate that there are 'newer' therapies out there as alternatives. Nitrate patches, shock wave (lithotripsy), glucosamine and injections of polidocanol, glucose, autologous blood, aprotinin, hyaluronic acid and even botulinum toxin may have

a place in the management of sports injuries and musculoskeletal pain.

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For further reading:

Bisset L, Beller E, Jull G, Brooks P, Darnell R, Vicenzino B. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: randomised trial. *BMJ*. 2006 Nov 4;333(7575):939.

<http://www.bmjjournals.org/cgi/content/full/333/7575/939>

Paoloni JA, Orchard JW. The use of therapeutic medications for soft-tissue injuries in sports medicine. *Med J Aust* 2005; 183: 384-388.

http://www.mja.com.au/public/issues/183_07_031005/pao10246_fm.html