Should non-steroidal anti-inflammatory drugs be given to orthopaedic patients with fractures?

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful adjuncts in perioperative pain relief. They act by inhibiting the activity of the enzyme cyclooxygenase (COX) which catalyses the formation of prostaglandins from arachidonic acid (Peck and Williams, 2000). COX exists as two isoenzymes, COX-1 and COX-2. COX-1 is responsible for the production of prostaglandins that form the protective gastric mucosal barrier, help maintain renal perfusion and regulate haemostatic function. COX-2 facilitates the inflammatory response. The beneficial actions of NSAIDs are associated with inhibition of COX-2 while the adverse effects are associated with inhibition of COX-1. NSAIDs are sub-divided into three main groups: non-specific COX inhibitors, preferential COX-2 inhibitors and specific COX-2 inhibitors. COX-2 is also responsible for the production of prostaglandins by osteoblasts which are essential for bone repair (Raisz, 2001). NSAIDs are therefore implicated in delayed fracture healing or non-union of fractures.

The case against NSAIDs

Multiple animal experiments have demonstrated that NSAIDs delay fracture healing (Bandolier, 2004). Drugs implicated include indomethacin, ibuprofen, celecoxib, ketorolac and parecoxib. One study demonstrated that while delays in bone repair were reversible with stopping indomethacin, this was not the case with ibuprofen (Altman et al, 1995).

Animal experiments aside, a dose-dependent relationship between non-union and ketorolac has been demonstrated in patients undergoing posterior spinal fusion. In one study, non-union rates were doubled to 25% if the patient smoked in addition to receiving ketorolac (Bandolier, 2004). Those that argue that ketorolac is unavailable in many anaesthetic rooms are reminded that diclofenac and ketorolac are both from the same class of NSAIDs, i.e. acetic acid derivatives.

Increased non-union in long-bone fractures has been demonstrated when indomethacin was given to patients for heterotopic bone formation prophylaxis, and when NSAIDs were prescribed for patients following intramedullary femoral nailing (Bandolier, 2004). In addition, a study of prescription use in 9995 patients with humeral fractures showed non-union is associated with longer term NSAID use (Bhattacharyya et al, 2005).

The case for NSAIDs

The animal evidence is contradictory. For example, celecoxib was shown postoperatively in rats to actually increase fibrous healing (Brown et al, 2004). The difficulty with animal experiments is trying to extrapolate the findings to humans. A randomized controlled trial of Colles' fractures aimed to confirm this inhibitory effect in man. However, in this study piroxicam had no effect on bone density and did not decrease fracture healing (Bandolier, 2004).

Ketorolac has a marked effect on bone healing compared to other NSAIDs. Reuben's (2001) study of posterior spinal fusion patients showed that the non-union rate with rofecoxib and celecoxib was as low as those who did not receive NSAIDs. However, ketorolac in the same study had a much higher rate of fracture non-union.

The study of prescription use, mentioned above, that identified longer term use of NSAIDs to be associated with non-union is likely to reflect the use of analgesics by patients with painful non-healing fractures. A large retrospective cohort study in which NSAIDs were prescribed for over 500 000 patients demonstrated no major effect on fracture risk (Van Staa et al, 2000).

Bone resorption can be affected through prostaglandin inhibition. This implies that NSAIDs could actually reduce bone loss. One study demonstrated that bone density was higher in NSAID users and their fracture risk was unaffected. An additional study showed that concomitant use of COX-2 inhibitors and aspirin was associated with higher bone density. Multiple authors have demonstrated higher rates of delayed healing or non-union, and hip fracture in smokers. Smoking cessation may well be more significant than avoiding NSAIDs altogether (Bandolier, 2004).

Conclusions

NSAIDs affect prostaglandin production and many studies have demonstrated a detrimental effect on bone healing. However, the evidence is conflicting and further studies are clearly required. Short-term use can still be justified in simpler fractures as there is not enough clinical evidence to deny patients their analgesic benefits. This is especially so if the surgical preference is to avoid peripheral nerve blockade for risk of missing the symptoms of compartment syndrome. However, for complicated non-unions, such as those referred to specialist centres for spatial frames, NSAIDs should be avoided. BJHM

Dr Andrew Williams *is Specialist Registrar in the Department of Anaesthesia, The Royal London Hospital, London E1 1BB*

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Anaesthetic and critical care dilemmas are coordinated by Dr John Orr and Dr Annie Hunningher, Research Fellows at the Centre for Anaesthesia, UCL, London Ideas for future dilemmas can be sent to Rebecca Linssen bjhm@markallengroup.com