

NSAIDs

Can they do more harm than good?



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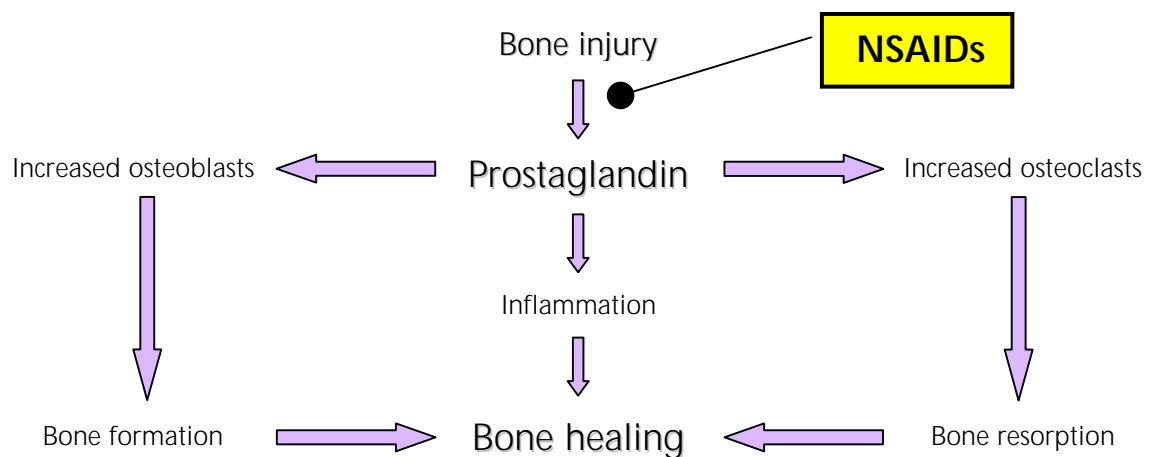
NSAIDs – the hidden pitfalls

NSAIDs have a pharmacology that targets inflammatory processes, acting to decrease the synthesis of eicosanoid mediators (eg. prostaglandins and thromboxane families of compounds) through inhibition of cyclooxygenase (COX) enzymes and thereby lead to alleviation of clinical signs. However, traditional NSAIDs, which mostly target both forms of cyclooxygenases, COX-1 and COX-2 (i.e. nonselective NSAIDs), are known to have common and serious gastrointestinal side effects.

To avoid these adverse effects, selective COX-2 inhibitors were developed as COX-2 expression was thought to be specific to

sites of inflammation. Despite diminished gastrointestinal side effects, a number of hidden pitfalls in using COX-2 inhibitors are now emerging. Important roles for COX-2 in the resolution of inflammation and the healing process are now evident. Indeed, as prostaglandins have diverse functions, including blood clotting, nerve growth, wound healing, kidney function and blood vessel tone, it follows that NSAID treatment may have unwanted and serious side effects. Indeed, *in vivo* and *in vitro* studies of NSAIDs have demonstrated adverse effects on the healing of bone, cartilage, eye, ligament, skin, tendon, tendon to bone and ulcers. [1]

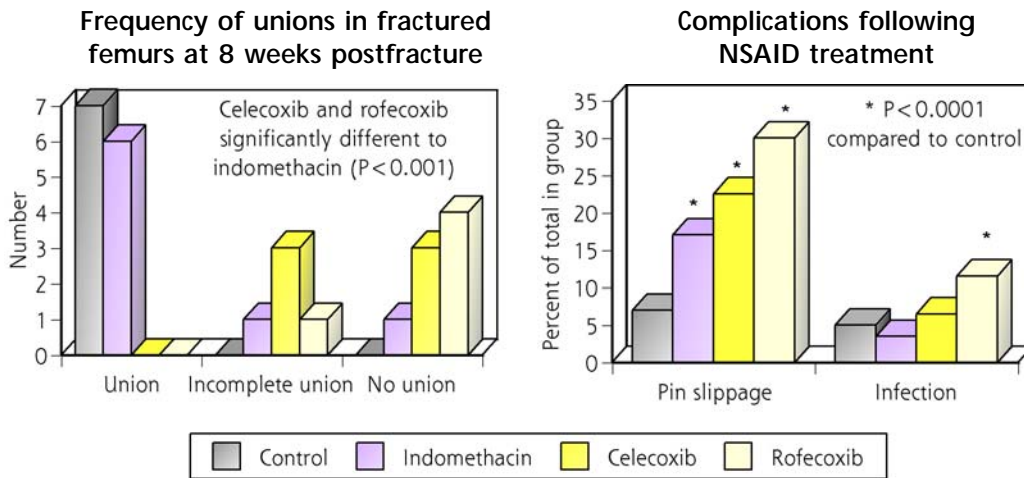
Prostaglandins are essential for bone healing



When bone trauma occurs the local blood supply to the bone is disrupted leading to death of the cells in the area. The healing process is initiated by an inflammatory response followed by bone resorption and bone production. The inflammatory response is key to the healing process as it results in the release of vasoactive angiogenic pyrogens required for healing.

Prostaglandins are integral to bone healing as they elicit and participate in inflammatory responses, increase osteoclast activity and subsequent bone resorption and increase osteoblast activity and new bone formation. It is therefore likely that NSAIDs by inhibiting the COX enzymes and prostaglandins also inhibit bone healing. [2]

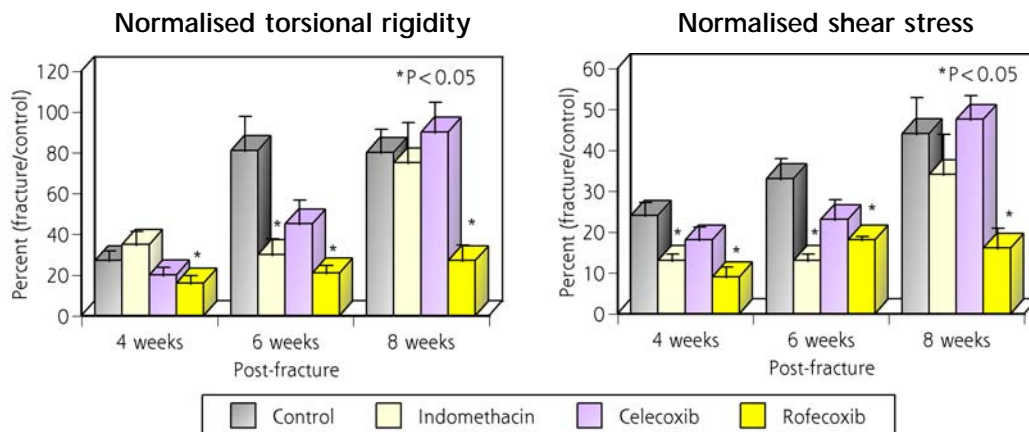
COX-2 activity is necessary for fracture healing



It has been demonstrated in rats that fracture healing fails following treatment with the COX-2 selective NSAIDs, celecoxib (4mg/kg) and rofecoxib (3mg/kg). Treatment with indomethacin (1mg/kg), a nonselective NSAID, was found to delay but not prevent fracture healing. Radiograph analysis of the fractured femur showed

bridging of the fracture gap at 5-6 weeks in the indomethacin group compared to 4-5 weeks in the control, while the original fracture was still evident after 8 weeks in the celecoxib and rofecoxib groups. Pin slippage was a severe complication following NSAID treatment with 30% of rofecoxib treated rats affected. [3]

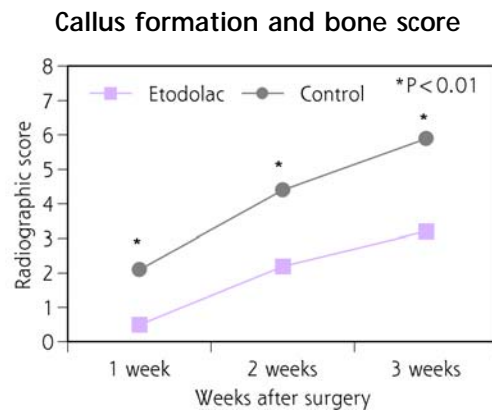
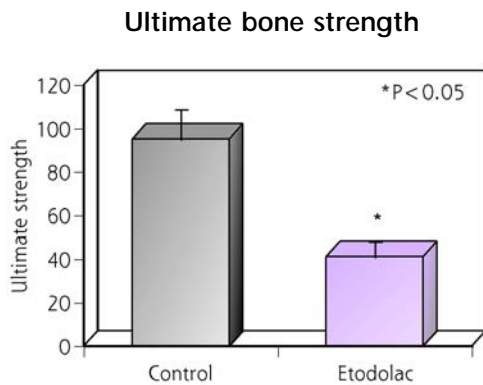
NSAIDs reduce the mechanical properties of bone



Indomethacin (1mg/kg), a nonselective NSAID and the selective COX-2 inhibitors, celecoxib (4mg/kg) and rofecoxib (3mg/kg) can alter the mechanical properties of fractured femurs in rats. The mechanical functioning of bone in rofecoxib treated rats was drastically reduced at 8 weeks post-fracture compared to controls. The rats had only obtained 45, 29 and 16% of peak torque (maximum twisting force), torsional rigidity (resistance to torque) and maximum

shear stress (ultimate shearing force withstood before failure) of the unfractured femurs respectively indicating healing failure. Treatment with indomethacin or celecoxib reduced mechanical properties of the fracture site at early time points however by 8 weeks values were similar to controls. The low torsional rigidity and shear stress at 6 weeks post-fracture in these groups indicated that the fracture site had not been bridged with bone. [3]

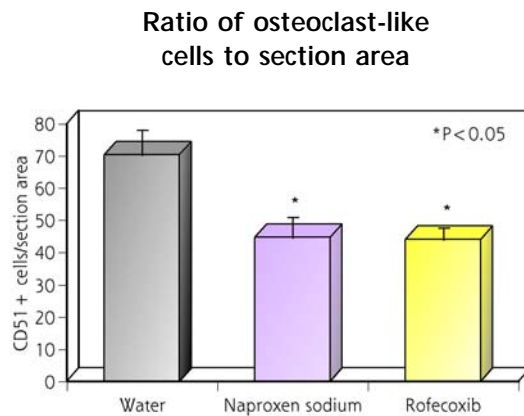
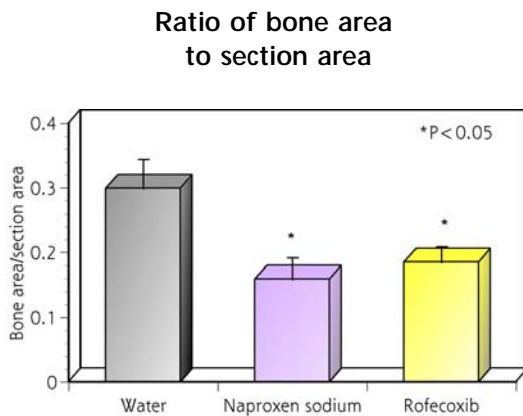
NSAIDs inhibit bone healing



Mounting evidence from animal studies indicates that NSAID treatment impairs fracture healing due to the inhibition of COX-2. Rats with closed non-displaced fractures at the middle of both femoral shafts were treated daily with 20mg/kg etodolac, a selective COX-2 inhibitor, or a vehicle control for three weeks.

Radiographs demonstrated that bone union and callus formation were delayed by the administration of the NSAID, etodolac. The ultimate strength and stiffness of etodolac treated femurs were significantly lower than controls indicating that mechanical maturation was inhibited by etodolac. [4]

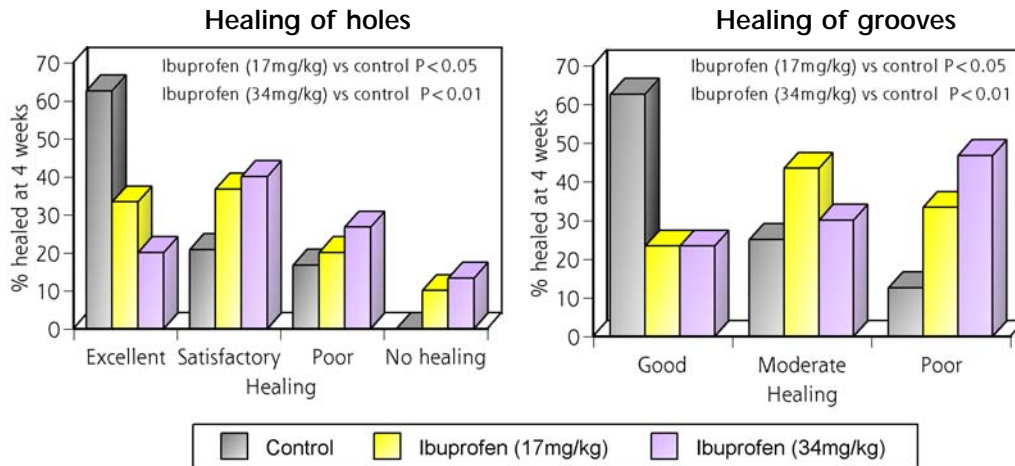
NSAIDs suppress bone formation



In a rabbit harvest chamber model, 4 weeks oral treatment with naproxen sodium, a nonselective NSAID (110mg/kg/day), and rofecoxib, a selective COX-2 inhibitor (12.5mg/day), significantly decreased bone ingrowth compared to water (control). Bone ingrowth was reduced from 29.9% following treatment with water to 15.9% and 18.5% when treated with naproxen

sodium and rofecoxib respectively. The number of osteoclast-like cells was also significantly decreased by both treatments. Rofecoxib treatment resulted in significantly less osteoblasts compared to controls. Together these results suggest that NSAIDs suppress bone formation and delay fracture healing. [5]

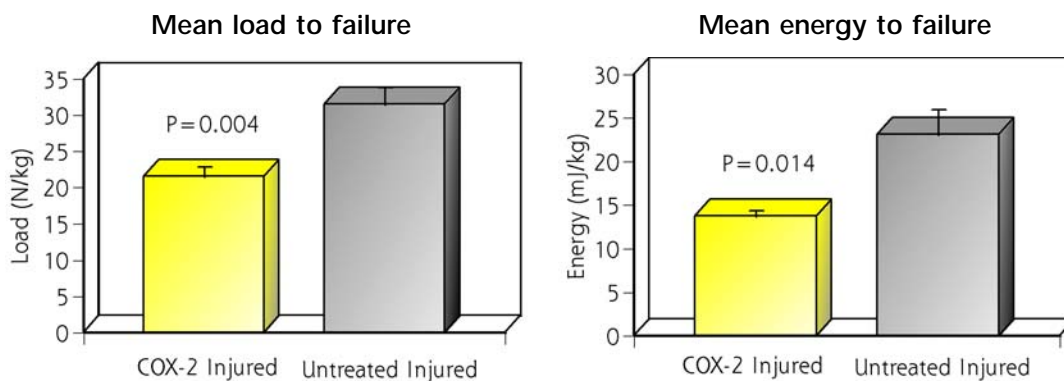
NSAIDs interfere with the healing of cartilage



Forty two rabbits underwent surgery to create a groove and a hole in the articular surface of both mandibular condyles. Fifteen rabbits received a daily dose of 17mg/kg and 15 rabbits received a daily dose of 34 mg/kg of ibuprofen, a nonselective NSAID, for 28 days. The remaining 12 rabbits were unmedicated and served as a control group. Examination after 4 weeks revealed that all holes in the control group had healed, while 10% and 13.3% of holes in the 17mg and 34mg/kg ibuprofen

groups did not heal. 12.5% of control animals showed poor healing of the grooves, as measured by observation of limited amounts of new bone and cartilage, compared to 33.3% and 46.7% in the 17mg/kg and 34mg/kg ibuprofen groups. Healing of holes and grooves was significantly different to control animals ($P < 0.05$), indicating that ibuprofen adversely effects the healing of bone and cartilage. [6]

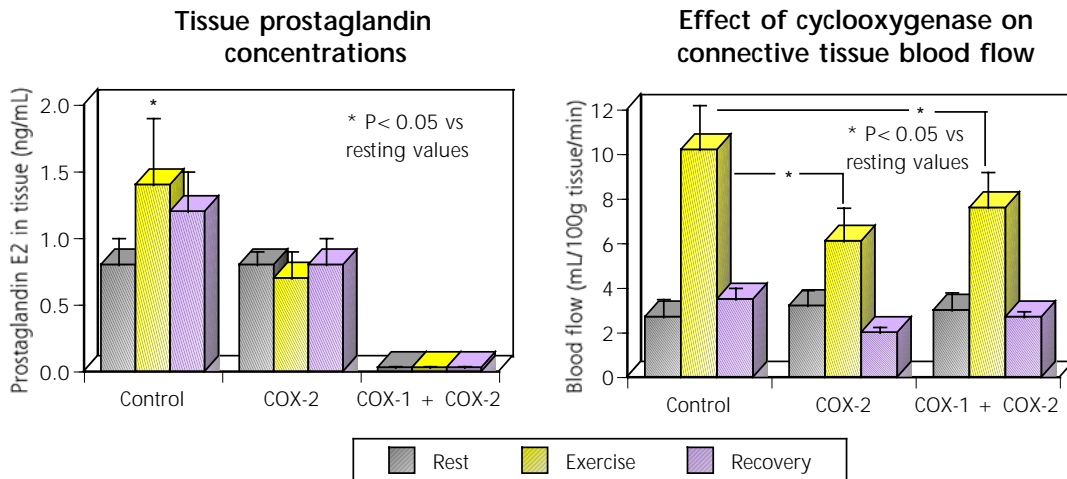
NSAIDs weaken ligament healing



In a surgically transected rat medial collateral ligament model it has been shown that celecoxib, a selective COX-2 inhibitor, interferes with ligament healing. Twenty-five rats were administered celecoxib in the established effective dose range of 5 to 30mg/kg per day for 6 days post-surgery. A further 25 rats received no treatment post-surgery. Fourteen days after surgery, the

rats were sacrificed and celecoxib treated ligaments were found to be significantly weaker than untreated ligaments ($P < 0.05$). In the celecoxib treated groups, the strength of ligaments was 32% less and the energy absorbed by ligaments was 41% less than untreated ligaments suggesting that COX-2 inhibitors should be prescribed with caution for ligament injuries. [7]

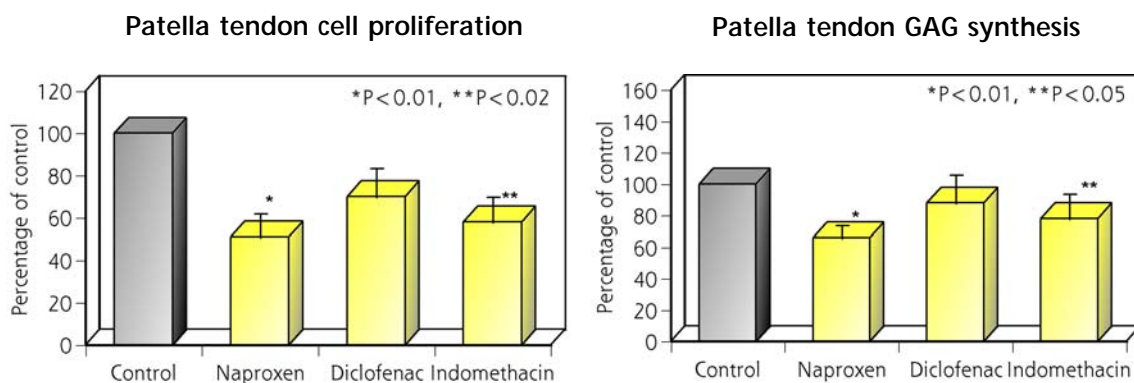
NSAIDs reduce blood flow in connective tissue



A COX-2 specific mechanism, inducible during mechanical tissue stress, is responsible for increased tissue prostaglandin synthesis during exercise in humans. Increase in tissue prostaglandin plays an important role for blood flow in peritendinous connective tissue during muscular contractions and physical loading *in vivo*. Treatment with celecoxib, a

selective COX-2 inhibitor and indomethacin, a nonselective NSAID, reduced blood flow in connective tissue during exercise by 35 and 43% respectively. "This observation may have implications for the mechanism by which cyclo-oxygenase-blocking drugs influence both healthy and diseased tendon tissue". [8]

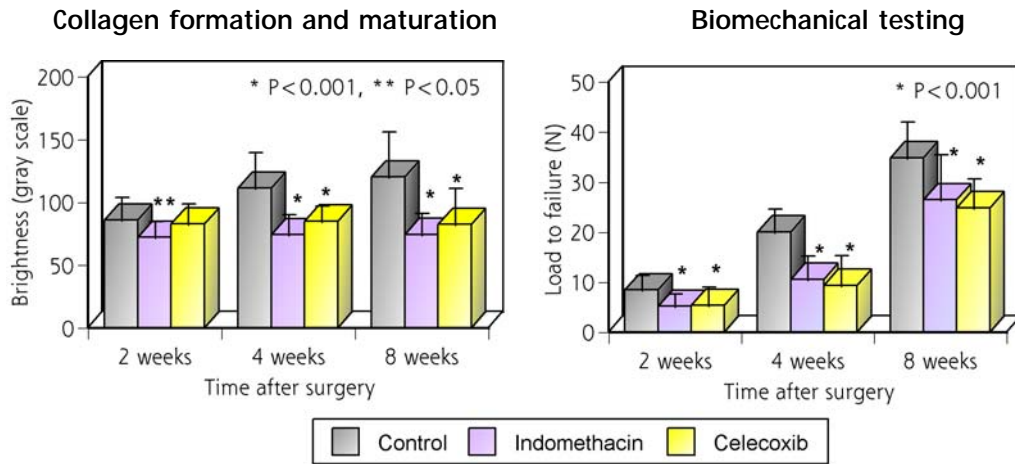
NSAIDs harm tendon repair



In an *in vitro* model of human tendon metabolism, pharmacological concentrations of the nonselective NSAIDs, indomethacin and naproxen inhibited tendon cell proliferation and glycosaminoglycan (GAG) synthesis. Cell proliferation was inhibited to 58% and 51% by indomethacin and naproxen respectively. GAGs are major constituents of proteoglycans which form part of the tendon matrix. Proteoglycans

modulate the formation of collagen fibres and play a major role in the repair process. GAG synthesis was inhibited to 78% and 66% of control values by indomethacin and naproxen respectively. The findings indicate that NSAID treatment may be harmful to tendon repair and should be used with caution when treating pain after tendon injury and surgery. [9]

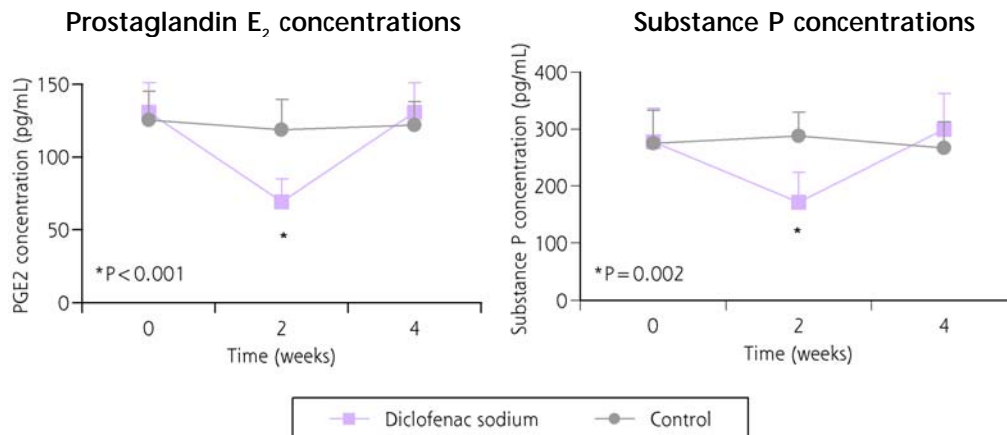
NSAIDs impair tendon-to-bone healing



Celecoxib, a selective COX-2 inhibitor, and indomethacin, a nonselective NSAID, have been shown to significantly inhibit tendon-to-bone healing in rats undergoing acute rotator cuff repair. Sixty rats were treated post-operatively with 14 days of celecoxib, 60 rats with indomethacin and 60 rats remained untreated. Biomechanical testing of load to failure demonstrated that tendon-to-bone strength in NSAID treated rats was

significantly less than untreated controls with a 24% and 29% lower load to failure following indomethacin and celecoxib treatment respectively compared to controls 8 weeks after surgery. Histological analysis revealed significantly less collagen formation and maturation compared to controls at all weeks following indomethacin treatment and at 4 and 8 weeks following celecoxib administration. [10]

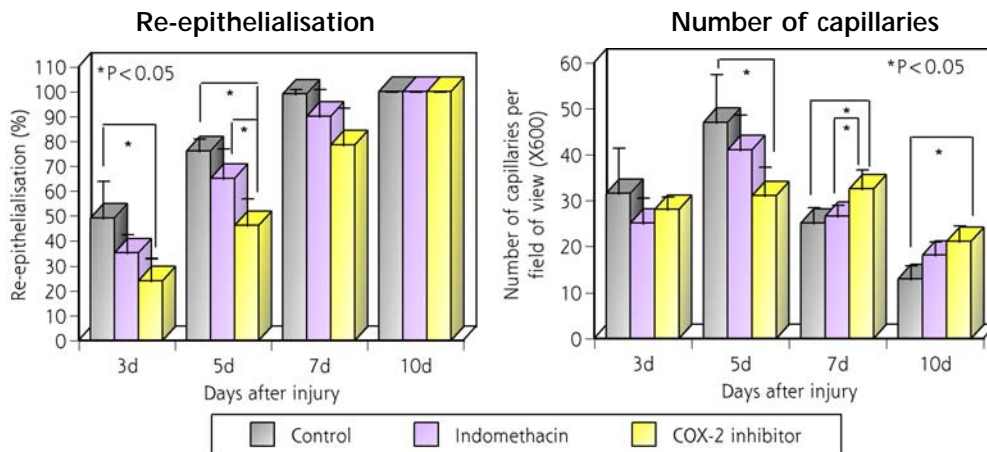
NSAIDs lead to corneal complications



Topical diclofenac sodium, a nonselective NSAID, is frequently used in ophthalmology practice. A study of 10 healthy volunteers treated with 0.1% diclofenac sodium eyedrops 3 times daily for 2 weeks, demonstrated that NSAID use results in reduced concentrations of prostaglandin E₂ (PGE₂) and Substance P in tears. Treatment with diclofenac sodium reduced PGE₂ from 130.8 to 69.1 pg/mL and Substance P

concentrations from 278 to 171.7 pg/mL after 2 weeks treatment. Concentrations had returned to baseline values 2 weeks after treatment had ceased. Diclofenac sodium should be used with caution in eye disease as damage to the corneal epithelium has been reported following its use and the depletion of Substance P may lead to corneal complications. [11]

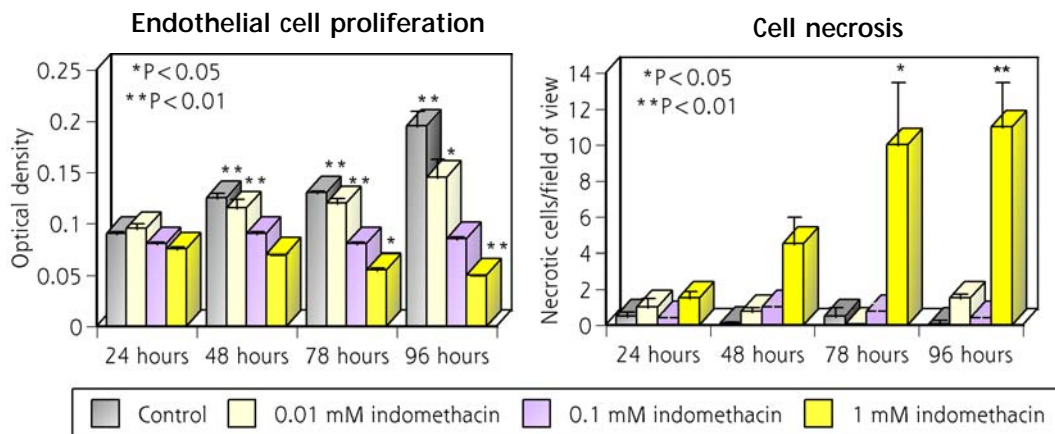
NSAIDs delay cutaneous wound healing



Studies indicate that prostaglandins are essential for cutaneous wound healing. A study in rats following excisional injury in the skin demonstrated a marked induction of COX-2 beginning 12 hours and peaking 3 days after injury. When rats were administered a COX-2 inhibitor NS-398 (5mg/kg/day), a significant delay in re-epithelialisation and the peak of

angiogenesis in the early phase of wound healing was noted. Administration of a nonselective NSAID, indomethacin (0.5mg/kg/day), also resulted in delayed re-epithelialization [12]. In the dog, wound healing problems have been observed following postoperative application of meloxicam and indicate that such use should be restricted to 3-4 days [13].

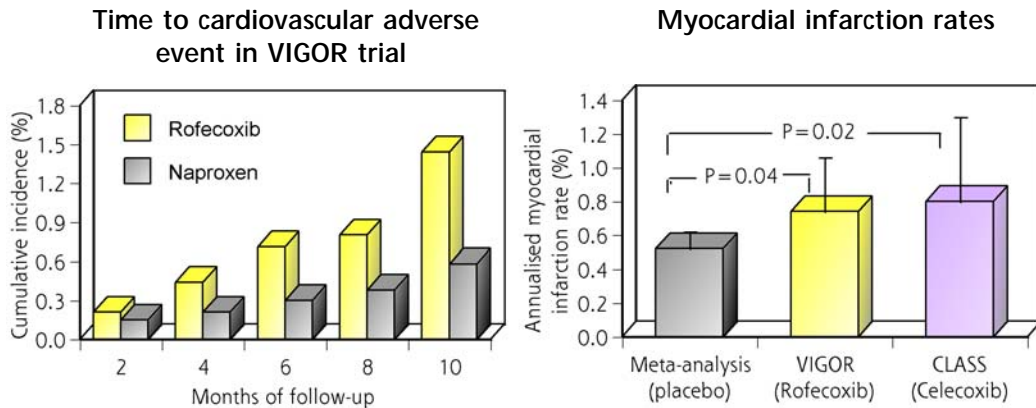
NSAIDs delay ulcer healing



In an *in vitro* model using drug concentrations comparable to human doses, treatment with the non selective NSAID, indomethacin (1mM), significantly inhibited dermal microvascular endothelial cell proliferation at 48, 72 and 96 hours compared with 24 hours and resulted in a significant increase in necrosis at 72 and 96 hours. Treatment with aspirin (1mM) also significantly inhibited cell proliferation.

The antiproliferative effects of these NSAIDs were found to be unrelated to prostaglandin levels suggesting that a mechanism independent of prostaglandins is responsible for their effects on cell proliferation. Endothelial cell proliferation is integral to angiogenesis, a process fundamental to healing. Therefore NSAID inhibition of endothelial cell proliferation may delay ulcer healing. [14]

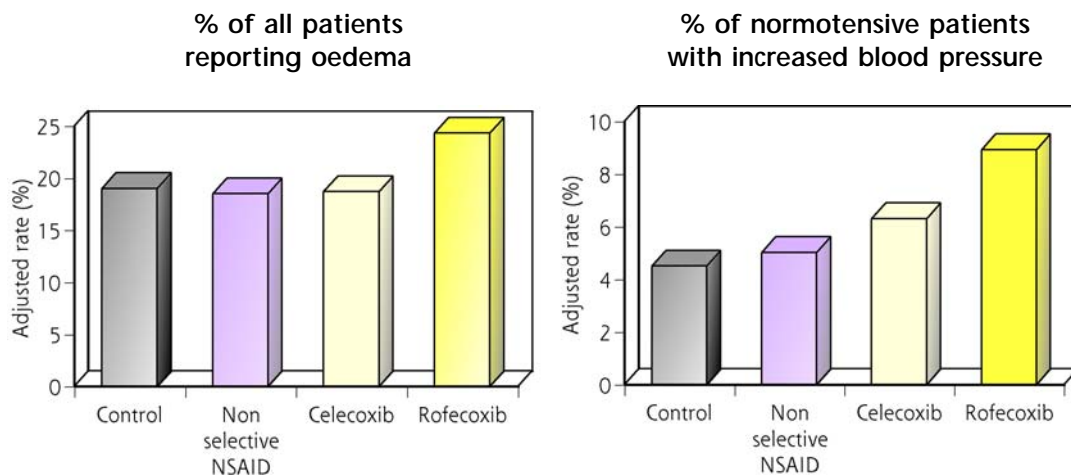
NSAID link to cardiovascular events



The worldwide withdrawal of the human COX-2 rofecoxib, due to increased risk of cardiovascular events highlights one of the hidden pitfalls of NSAID use. A multicentre placebo controlled trial confirmed a risk of cardiovascular events including heart attack and stroke beginning after 18 months of treatment [15]. This followed the findings of the VIGOR clinical trial reporting a significantly greater incidence of myocardial

infarction following rofecoxib treatment compared to naproxen (0.4% vs 0.1%) [16]. Myocardial infarction rates for rofecoxib and celecoxib were found to be significantly higher than placebo as determined by meta-analysis of 23407 patients. COX-2 inhibitors may increase cardiovascular events by interfering with the balance between prothrombotic thromboxane A₂ and antithrombotic vascular prostacyclin. [17]

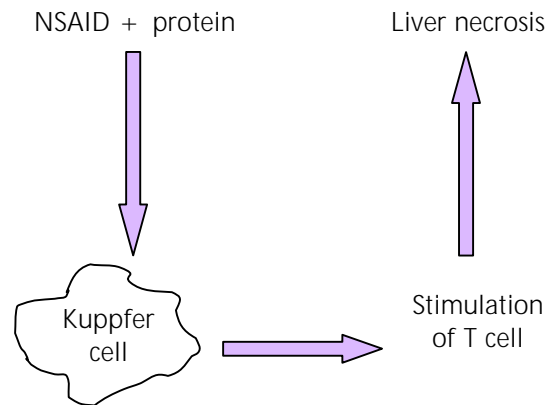
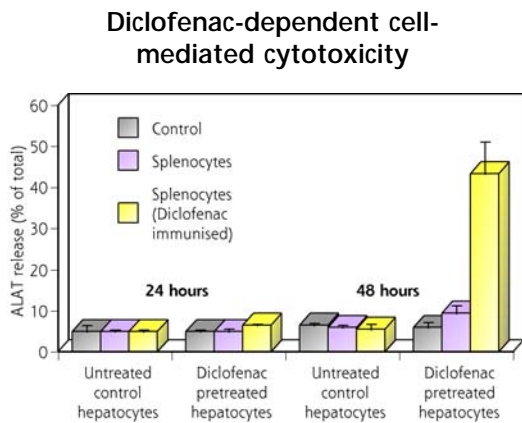
NSAIDs increase risk of oedema and hypertension



Investigation of 8538 patients using a nonselective NSAID, celecoxib or rofecoxib exclusively, for treating rheumatoid arthritis or osteoarthritis demonstrated that rofecoxib use increases oedema and hypertension compared to nonusers of NSAIDs (control). When rates were adjusted for age, sex and rheumatoid arthritis, it was found that rofecoxib users were 1.37 times more likely

to report oedema than nonusers ($P < 0.001$). Rofecoxib treatment was significantly associated with a blood pressure increase in both hypertensive and normotensive patients ($P < 0.001$). Hypertensive patients were 1.55 times more likely and normotensive patients 2.08 times more likely to have increased blood pressure compared to nonusers. [18]

NSAIDs may induce liver cytotoxicity

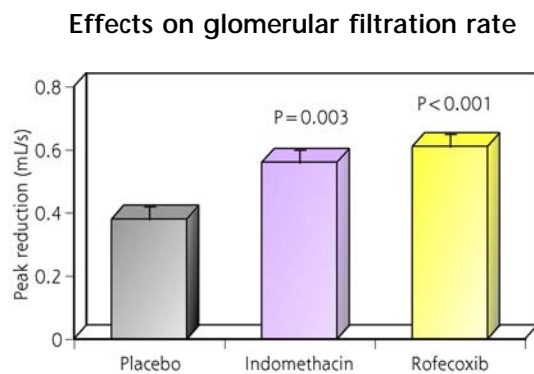


Hepatocellular toxicosis has been associated with carprofen treatment in the dog. Analysis of results from 21 dogs supported an idiosyncratic cytotoxic hepatocellular reaction [19]. In mice, cell-mediated cytotoxicity of hepatocytes has been demonstrated in the presence of diclofenac. Cultured mice hepatocytes were pre-exposed to non-toxic levels of diclofenac and co-cultured with splenocytes (monocyte characteristic of splenic tissue) from mice

immunised with a synthetic diclofenac-protein adduct. Alanine aminotransferase (ALAT) was dramatically increased, after 48 hours co-culture in cultures pre-treated with diclofenac indicating hepatocyte injury. No dramatic increases in ALAT were seen in controls. The results imply a role for T-cells in diclofenac-dependent cytotoxicity and may support the concept of immune mediated damage to the liver as a result of NSAID treatment [20].

COX-2 activity is important for renal function

It was hoped that the development of COX-2 selective inhibitors would reduce the known adverse renal effects associated with traditional NSAIDs. However, evidence from animal and human studies suggests that selective COX-2 inhibitors are equal to traditional NSAIDs in causing nephrotoxicity [21]. COX-2 is constitutively expressed in the kidney and COX-2 metabolites may be involved in maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion. In a study of 15 elderly patients, single doses of rofecoxib (250mg), a selective COX-2 inhibitor, and indomethacin (75mg), a nonselective NSAID, significantly decreased the glomerular filtration rate by 0.23mL/s and 0.18mL/s respectively compared to placebo. Both treatments caused significant peak reduction in creatinine clearance (0.32 and 0.19mL/s respectively, $P=0.002$ and



0.051) and in urinary sodium excretion (68.35% and 48.95% respectively, $P<0.001$ and $P=0.005$) compared with placebo. Changes in serum electrolyte levels were similar between rofecoxib and indomethacin. These findings indicate that COX-2 inhibitors affect renal function similarly to traditional NSAIDs and therefore the same precautions should be taken when prescribing them [22].

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NSAIDs are proven to adversely affect:

- Bones
- Cardiovascular Function
 - Eyes
 - Ligaments
 - Liver
 - Skin
 - Tendons
- Tendon to Bone

In addition to the infamous affects on

- Gastrointestinal tract
 - Kidneys



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