Non-steroidal anti-inflammatory drugs inhibit bone healing: A review

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Keywords
Non-steroidal anti-inflammatory drugs, NSAID, bone healing

Summary
The ability of non-steroidal anti-inflammatory drugs (NSAID) to inhibit bone healing has been established in experimental animal models using mice, rats, and rabbits. The mechanism of action is largely unknown but stems from prostaglandin inhibition and is likely multifactorial. In human medicine NSAID are known to prevent heterotopic ossification, however the clinical importance of their effects on bone healing remains controversial. Although a small handful of reports suggest that NSAID suppress bone healing in dogs and horses, there is little published information to direct veterinary practice in domestic species.

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Vet Comp Orthop Traumatol 2010; 23: 385–392
doi:10.3415/VCOT-10-01-0017
Received: January 31, 2010
Accepted: June 23, 2010
Pre-published on: September 9, 2010

Introduction

The mechanism of action of non-steroidal anti-inflammatory drugs (NSAID) had only recently been discovered when the drugs' ability to inhibit bone healing was first documented. In 1976, Ro and others reported significantly reduced fracture healing in rats treated with indomethacin (1). In the same year, a 64-year-old man with an ankle fracture/luxation was purposefully treated with indomethacin to prevent callus formation in anticipation of surgery (2). The authors noted, "A displaced fibular fracture usually heals even without external immobilisation. In the present case, however, the fracture did not unite in spite of external immobilisation for nine weeks."

These initial reports led to a flurry of research which was periodically excited and directed by subsequent discoveries such as cyclooxygenase-2 (COX-2) and the biological mechanisms of bone healing. Today, NSAID are recognised as being effective inhibitors of bone formation in experimental models of fracture healing, spinal fusion, bone ingrowth into implants, mechanically induced bone remodelling, and heterotopic ossification (3). This review focuses on the effects of NSAID on bone healing after injury.

Mechanism of inhibition

In 1971 Vane and others discovered that aspirin, indomethacin, and salicylate exert their potent antiphlogistic effects by inhibiting COX, the rate-limiting enzyme in prostaglandin synthesis (4). Prostaglandins, small signalling molecules with paracrine and autocrine activity, have since been shown to regulate constitutive and inducible functions throughout the body, including bone healing (5–9). The mechanism of NSAID inhibition to bone healing is unknown, but is likely multifactorial. Researchers have suggested that NSAID affect normal bone healing in multiple ways, with emphasis often (but not exclusively) placed on processes related to the inflammatory stage.

Deciphering the mechanism of NSAID inhibition requires an understanding of fracture healing. Fracture healing presents an exquisitely orchestrated series of coordinated molecular and cellular events. Before the molecular mechanisms of bone healing were appreciated, careful histological observations characterised the temporal stages of bone healing (10, 11).

Direct (primary) fracture healing is characterised histologically by osteonal 'cutting cones' directly crossing the fracture gap, bypassing the intermediate stages of cartilaginous callus and endochondral ossification (10–12). This type of healing is possible only with direct bone contact and rigid stabilisation. Osteonal activity increases near the injury – this phenomenon is referred to as 'regional acceleratory phenomenon' (RAP) and probably plays an important role in direct fracture healing (12). The mechanism of RAP is unknown, but the phenomenon may be mediated by the same signalling molecules as seen in other types of tissue repair (12).

Indirect (secondary) fracture healing can be classified into four histologically observable overlapping phases: inflammatory, chondrogenic, osteogenic, and remodelling (10, 13). The inflammatory phase is characterised by haematoma formation, local tissue hypoxia, and increased local production of inflammatory cytokines and growth factors, including prostaglandins (6, 14). Mesenchymal stem

cells are recruited from intra- and extra-osseous tissues to differentiate into chondrogenic and osteogenic cell types. In the chondrogenic phase, a cartilaginous callus bridges the fracture fragments and intramembranous ossification occurs under the periosteum at the fracture edges. In the osteogenic phase, the cartilaginous callus is replaced by woven bone via endochondral ossification in a process reminiscent of physeal growth. In the remodelling phase, young woven bone is replaced by lamellar bone to restore mechanical integrity.

The molecular mechanisms of bone healing are complex and are the subjects of current ongoing studies. Local and systemic regulatory molecules including cytokines, growth and differentiation factors, hormones, and extracellular matrix molecules regulate processes such as cellular migration, proliferation, differentiation, extracellular protein synthesis, and apoptosis (15). The most important local molecules currently recognised in fracture healing can be divided into three categories: 1) pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), platelet-derived growth factor (PDGF), and others; 2) transforming growth factor-beta superfamily members, which include bone morphogenetic proteins (BMP), transforming growth factor beta isoforms (TGF-β), growth differentiation factors (GDF), activins, inhibins, and Müllerian inhibiting substance; and 3) angiogenic factors, including vascular endothelial growth factor (VEGF) and angiopoietins (15, 16). Although there is considerable overlap, these local molecules are expressed in distinct temporal (and spatial) patterns which can be loosely correlated to the histological stages of fracture healing (14, 16). In general, inflammatory cytokines are elevated in the inflammatory phase and partially during secondary bone formation in the remodelling phase. Some members of the TGF-β superfamily, such as bone morphogenetic protein-2 (BMP-2), are expressed at all stages of healing whereas others are elevated at more specific times, such as during the cartilaginous phase (TGF-β) or during the osteogenic phase (BMP-3, -8). Angiogenic factors, though present throughout fracture healing, are most prominent during endochondral ossification in the osteogenic phase (16).

Although the mechanism for NSAID-induced bone healing inhibition is unknown, the predominant theory supposes that NSAID, by inhibiting prostaglandin synthesis, interfere with cell signalling during the inflammatory phase leading to an uncoordinated healing response. Endogenous prostaglandins E and F increase locally in the first seven days after fracture, suggesting a signalling function by prostaglandins in the early healing period (6–8). Attempts to simplify prostaglandin's effects on bone have been frustrated by the difficulty in simulating their naturally occurring expression and environment *in vitro*. The small, quickly metabolised and locally acting molecules can promote bone resorption, bone formation, or both depending on the extracellular environment and the intracellular chemical milieu (9). Exogenous prostaglandin E administration increases regional acceleratory phenomenon after rib fractures in dogs, increasing both resorption and production in response to injury (17, 18). Synthetic prostaglandin receptor agonists have an overall anabolic effect and enhance bone healing in rats and dogs in experimental conditions (19, 20).

Inhibitory effects on mesenchymal stem cell differentiation and activity have been proposed as a mechanism for NSAID-induced bone inhibition (21–23). In a notable *in vivo* study involving an NSAID, diclofenac profoundly reduced the number of histologically visible osteoblasts at the injury site 10 days after bone drill defects were created in rat femora, suggesting inhibition of osteoblast differentiation or migration (23). Tibial fracture calluses in mice lacking COX-2 expression (COX-$2^{-/-}$) had markedly fewer histologically visible osteoblasts and a higher incidence of fibrous nonunion compared with wild-type mice (21). In a cell culture model by the same authors, bone marrow cells from COX-$2^{-/-}$ mice failed to differentiate into osteoblasts to the same degree as cells from wild-type mice when stimulated by osteogenic molecules. The addition of prostaglandin E_2 (PGE_2) restored osteoblastogenesis to wild-type levels. Bone morphogenetic protein-2 also induced osteoblastogenesis in both wild type and COX-$2^{-/-}$ cell cultures to approximately the same degree. The authors suggested that BMP-2 may be downstream to prostaglandins during osteoblastogenesis and bone formation (21).

Subsequent studies have investigated the relationship between COX-induced prostaglandin production and bone morphogenetic proteins. A selective COX-2 inhibitor reduced BMP-2 expression in human mesenchymal stem cells; this effect was reversed with the addition of PGE_2, suggesting COX-2 derived PGE_2 induces BMP-2 expression (24). Another study showed further support for this relationship, but indicated an opposite pathway in that BMP-2 induced COX-2 expression in cultured murine osteoblasts (25). In the same study, BMP-2-induced ectopic ossification was inhibited in COX-$2^{-/-}$ mice, indicating that BMP-2 effects on bone formation are in part due to COX-2 activation. Finally, immunohistochemistry detected a simultaneous rise in BMP-7 (also known as osteogenic protein-1, or OP-1) and COX-2 at fracture calluses in mice. In the same study, BMP-7-induced ectopic ossification was inhibited by diclofenac, an NSAID (26).

Inhibition of angiogenesis has also been suggested as a mechanism of NSAID effects on bone healing. Cyclooxygenase-2 metabolic products (mainly prostaglandins) are stimulators of angiogenesis, which is essential for fracture healing (27, 28). Rofecoxib inhibited osteotomy healing in mice femurs and significantly reduced blood flow within the femoral calluses (29). After analysing linear regression models, however, the authors concluded that rofecoxib's negative effect on blood flow was independent of rofecoxib's negative effect on bone healing.

In vivo evidence

Over thirty years of research have established that NSAID can slow fracture healing in rodents. Using closed simple transverse long-bone fractures in rats and mice, investigators have repeatedly documented bone healing inhibition as measured by gross examination, nonunion rates, radiographic scores, bone mineral density,

Table 1 Effect of non-steroidal anti-inflammatory drugs on rodent and rabbit models of bone healing.

Year, Author	Animal	Drug(s)	Results
1976, Ro (1)	Rats	Indomethacin	Decreased radiographical and histological healing, decreased mechanical strength of healed bone.
1979, Sudmann (57)	Rabbits	Indomethacin	Inhibited Haversian remodelling in response to osteotomy.
1980, Allen (47)	Rats	Indomethacin, Aspirin	Both drugs caused dose-dependent decrease in fracture callus histological healing score.
1980, Törnkvist (58)	Rats	Ibuprofen	Decreased dry weight, ash weight, and organic matter weight of healing bones.
1982, Elves (59)	Rats	Indomethacin	Decreased osteogenesis (strontium uptake) in response to drill defect.
1990, Keller (30)	Rabbits	Indomethacin	No effect on Haversian remodelling close to a 2 mm drill defect, measured six weeks after operation.
1998, Reikeraas (31)	Rats	Indomethacin, Ketoralac	Indomethacin weakened mechanical strength of healed fractures at 6 weeks; ketorolac had no effect at 6 weeks (3 days of treatment).
2002, Long (32)	Rabbits	Indomethacin, Celecoxib	Indomethacin lowered spinal fusion rate; celecoxib had no effect.
2002, Simon (35)	Rats, mice	Indomethacin, Rofecoxib, Celecoxib	**Part I:** Indomethacin delayed bone healing temporarily; rofecoxib and celecoxib had more permanent effects. **Part II:** Cox-$2^{-/-}$ mice had impaired bone healing.
2003, Beck (38)	Rats	Diclofenac	Decreased bone density and mechanical strength of healing bone.
2003, Gerstenfeld (34)	Rats	Ketorolac, Parecoxib	Ketorolac decreased bone healing (histology and mechanical testing); parecoxib showed variable results.
2003, Giordano (45)	Rats	Tenoxicam	Decreased fracture healing (histomorphometry).
2003, Riew (46)	Rabbits	Indomethacin	Decreased spinal fusion rate.
2004, Brown (36)	Rats	Indomethacin, Celecoxib	Both drugs decreased histological healing scores; only indomethacin had effect on mechanical strength.
2005, Goodman (41)	Rabbits	Rofecoxib	Decreased bony ingrowth into titanium chamber (histomorphometry).
2005, Endo (37)	Rats	Etodolac	Time and duration-dependent reduction in fracture healing (radiographic scores and mechanical testing).
2005, Persson (60)	Rats	Indomethacin	Decreased heterotopic bone formation, decreased mineralisation of traumatised femurs.
2006, Leonelli (42)	Rats	Rofecoxib, Ibuprofen	Rofecoxib decreased fracture healing (nonunion rate, radiographic score, histological score); ibuprofen had little effect.
2006, Murnaghan (29)	Mice	Rofecoxib	Decreased fracture healing and blood flow across fracture callus.
2007, Krischak (39)	Rats	Diclofenac	Duration-dependent decrease in fracture healing (histomorphometry).
2007, Gerstenfeld (8)	Rats	Ketorolac, Valdecoxib	Duration-dependent decrease in fracture healing (nonunion rate, mechanical testing).
2007, Simon (7)	Rats	Celecoxib	Dose- and duration-dependent decrease in fracture healing (nonunion rate, radiographic score, and mechanical testing).
2008, Dimmen (40)	Rats	Parecoxib	Transient reduction in bone mineral density during early healing phase (treatment for 7 days).
2009, Dimmen (43)	Rats	Indomethacin, Parecoxib	Both drugs reduced bone mineral density and mechanical parameters of healing fractures.
2009, O'Connor (61)	Rabbits	Ibuprofen, Rofecoxib	Rofecoxib reduced mechanical strength more than ibuprofen.
2010, Nyangoga (33)	Rabbits	Ketoprofen	No effect on osteoconduction induced by β-tricalcium phosphate graft in femoral epiphyseal defects.
2010, Spiro (26)	Mice	Diclofenac	Decreased fracture healing (micro-computed tomography, mechanical testing).

radiopharmaceutical uptake, histomorphometry, micro-computed tomography, and mechanical testing of fracture calluses (▶Table 1). The intensity and reliability of this inhibition raises concerns about the clinical ramifications of prescribing NSAID to other animals in the period following a fracture or orthopaedic procedure. Although conclusions are limited by experimental design and are sometimes conflicting, the current experimental data would suggest the following points:

- All NSAID studied to date have the potential to inhibit bone formation
- NSAID may have their greatest effect during the early phase of bone healing
- NSAID have a dose-dependent effect on bone healing
- NSAID often have duration-dependent and reversible effects on bone healing
- NSAID use before bone injury does not seem to adversely affect bone healing

All NSAID studied to date have the potential to inhibit bone formation

From time to time, an article of research is published which concludes that a particular NSAID does not, like other NSAID, inhibit bone formation (30–33). These studies are often followed by subsequent studies showing that with a different experimental design, the same drug can inhibit bone healing. For example, ketorolac (1 mg/kg/day) given for three days had no effect on callus mechanical strength measured six weeks after fracture in rats (31). However, ketorolac given at a higher dose (4 mg/kg/day) and for the entire time course of the experiment reduced mechanical strength and decreased histological scores of fracture calluses compared with untreated rats (34). Similarly, the authors of an experiment involving spinal fusion in rabbits concluded that while indomethacin reduced spinal fusion in their model (validating their study as one that can detect spinal fusion inhibition), celecoxib had no significant effect (32). In their discussion, these authors admitted that the pharmacokinetics of celecoxib in rabbits was unknown; the dose used in their study was extrapolated from recommended human dosages using allometric scaling calculations. This research was contrasted by a study involving femoral fractures in male rats, where celecoxib inhibited fracture healing as measured by radiographic scores and nonunion rate (35). Celecoxib failed to produce significantly different mechanical testing scores than in untreated rats, however. Four years later, the same authors showed that in *female* rats, celecoxib significantly delayed femoral fracture healing when measured by mechanical testing (7). In their discussion, the authors pointed out the discovery that intact male and female Sprague-Dawley rats have markedly different celecoxib metabolism, and that the plasma elimination half-life of celecoxib in female rats is nearly four times longer than that of male rats.

Cyclooxyenase-2 was discovered in 1991, and the first coxibs – NSAID designed specifically to be COX-2 selective – were released soon thereafter (5). Initial studies comparing selective to non-selective COX inhibitors argued that COX-2 selective NSAID did not have as profound an effect against bone healing as indomethacin, a traditional non-selective NSAID (32, 34, 36). Subsequent genetic and *in vivo* studies have provided strong evidence that inflammation stimulated by the COX-2 isoenzyme is essential for fracture healing, and that COX-2 selective NSAID have an equal or greater negative effect on fracture healing in rats than non-selective NSAID (7, 8, 21, 37–43). Thus, no single NSAID or group of NSAID has been cleared as being 'safe', or having no potential effect on bone healing.

Although adjusting the experimental design (increasing the dose or duration of NSAID treatment) allows researchers to illustrate fracture healing inhibition for almost any NSAID studied in rodent models, it is important to acknowledge that even fractures in the NSAID-treated groups often go on to heal. Additionally, it sometimes takes sensitive outcome measures (such as histomorphometry) to detect a significant difference between groups. It is impossible to make conclusions about clinical relevance in other species based on these studies.

Because most research in this field is geared towards human medicine, the most promising NSAID for use in humans at a particular time are studied (▶Table 1). Non-steroidal anti-inflammatory drugs frequently used in veterinary medicine such as carprofen, meloxicam, deracoxib, firocoxib, and flunixin have not been studied *in vivo*, with the exception of a recent abstract which evaluated carprofen in dogs (44).

NSAID may have their greatest effect during the early phase of bone healing

Rats given etodolac for only the first week after a femoral fracture had substantial decreases in radiographic scores and callus strength measured three weeks after the fracture (37). Their decreases were comparable to those of rats treated with etodolac for the entire three weeks of their healing period. In contrast, rats treated for only the last of three weeks had scores which were not significantly different from untreated rats. The seemingly permanent effects of short-term treatment with etodolac in this study contrast with those of subsequent studies in which the effects of short-term treatment with NSAID were reversible (7, 8, 39, 40). However, in agreement with this study, other studies also suggest that NSAID have their greatest inhibitory effect in the early inflammatory phase of bone healing (7, 38, 45, 46). Simon and others included a 'time delay' group in which rats were allowed to heal untreated for seven or 14 days after femoral fracture before receiving celecoxib for the rest of the 28 day study period (7). Rats in the group treated from seven to 28 days (21 day treatment duration) had higher radiographic scores and mechanical testing parameters at the study endpoint compared with rats treated from zero to 21 days (same treatment duration). However, in statistical analysis, the treatment groups were compared to untreated controls, and direct comparisons between the time delay and other treatment groups were not performed.

NSAID have a dose-dependent effect on bone healing

Few experiments include treatment groups that differ in NSAID dose, however those

that do suggest that a higher dose is more detrimental to bone healing. A dose-dependent decrease in histological scores was seen in fracture calluses from rats given indomethacin or aspirin (47). A dose-dependent decrease in radiographic scores and mechanical properties was also observed in fracture calluses from rats given celecoxib after femoral fractures (7).

NSAID often have duration-dependent and reversible effects on bone healing

Although some data suggest that effects of early NSAID administration can persist and be measured weeks after treatment has ended, there is also evidence that NSAID-induced inhibition is proportional to the duration of treatment, and that bone can heal normally once NSAID administration is discontinued (8, 37–41, 43). Calluses from rats given diclofenac for seven days after osteotomy were not histologically different than calluses from rats given placebo when evaluated at 21 days, whereas calluses from rats treated for the entire 21 days contained significantly less bone and more cartilage (39). Likewise, parecoxib given for seven days only transiently decreased bone mineral density after tibial fractures in rats – bone mineral density returned to normal by three weeks (40). In a three-part study involving ketorolac and valdecoxib, the authors not only noted a more detrimental effect from both drugs when given for longer durations – they also documented a drop in local prostaglandin E_2 at the fracture callus during treatment followed by a rise in prostaglandin E_2 after the drugs were discontinued (8). When measured seven days after NSAID discontinuation, local prostaglandin E_2 levels exceeded prostaglandin levels in untreated rats at the same time point after fracture, suggesting a rebound inflammatory effect.

NSAID use before bone injury does not seem to adversely affect bone healing

Simon and others included in their study a group of 23 rats that were treated with celecoxib for five days before femoral fracture in order to investigate whether NSAID would inhibit bone healing if discontinued at the time of bone trauma (7). This pre-treatment with celecoxib had little to no effect on fracture healing, suggesting that patients chronically taking NSAID, such as patients with osteoarthritis, would not suffer diminished bone healing as a result of the drug. Similar studies have not been performed to investigate the effects of longer or more chronic durations of pre-treatment.

Human clinical evidence

It is well-established that NSAID can prevent heterotopic ossification in humans. However, controversy remains regarding the clinical effects of NSAID on fracture healing and spinal fusion. Only a handful of clinical studies exist evaluating the effect of NSAID on fracture healing or spinal fusion in humans (▶Table 2).

Heterotopic ossification, or ectopic bone formation, commonly occurs in the soft tissues around the hip joint following hip surgery in humans. It is estimated that

Table 2 Clinical research investigating non-steroidal anti-inflammatory drugs (NSAID) and bone healing in humans.

Year, Author	Injury	Drug(s)	Results
Prospective clinical trials			
1988, Davis (52)	Distal radial fractures	Flurbiprofen	No effect on healing in patients treated with flurbiprofen for 2 weeks.
1993, Adolphson (51)	Distal radial fractures	Piroxicam	No effect on healing in postmenopausal women treated with piroxicam for 8 weeks.
2003, Burd (50)	Long-bone fractures	Indomethacin	Increased nonunion rate in patients treated with indomethacin for 6 weeks.
2005, Reuben (62)	Spinal fusion	Celecoxib	No effect on spinal fusion evaluated in 1 year in patients treated with celecoxib for 5 days after surgery. *Article retracted by publisher due to fabricated data.*
Retrospective observational studies			
1998, Deguchi (63)	Spinal fusion	Various NSAID	Increased nonunion rate in patients taking NSAID.
1998, Glassman (64)	Spinal fusion	Ketorolac	Increased nonunion rate by approximately 5 times in patients taking ketorolac.
2000, Giannoudis (65)	Femoral fractures	Various NSAID	Increased nonunion rate in patients taking NSAID.
2005, Bhattacharyya (53)	Humeral fractures	Various NSAID	Increased nonunion rate in patients taking NSAID or opioids 61-90 days after fracture.
2005, Reuben (66)	Spinal fusion	Celecoxib, Rofecoxib, Ketorolac	No effect on spinal fusion evaluated 1 year after surgery in patients treated for 5 days with celecoxib, rofecoxib, or low-dose ketorolac; increased nonunion rate in patients treated with high-dose ketorolac.
2008, Pradhan (67)	Spinal fusion	Ketorolac	No effect on spinal fusion evaluated 1 year after surgery in patients treated with ketorolac for 48 hours.

approximately one-third of humans undergoing total hip arthroplasty will develop some degree of heterotopic ossification, which can cause pain and reduced range-of-motion if moderate or severe (48). The etiopathogenesis is unknown, but stimulation by trauma or surgery suggests an inflammatory component. The ability of NSAID to inhibit heterotopic ossification has been recognised since 1977, and a recent meta-analysis concluded that medium to high doses of perioperative NSAID produce a substantial reduction in the incidence of radiographic signs of heterotopic ossification (48, 49). Non-steroidal anti-inflammatory drugs are commonly prescribed to high-risk patients to prevent heterotopic bone formation after hip surgery.

In a prospective, randomised, blinded clinical study involving trauma patients with acetabular fractures and concurrent long-bone fractures, 282 patients were allocated into three groups after open reduction and internal fixation of their acetabular fractures (50). One group received indomethacin for six weeks as prophylaxis against heterotopic ossification, while the other two groups received either no prophylaxis or a single dose of local radiation to the soft tissues around the hip joint. The patients receiving indomethacin had a significantly higher nonunion rate of their long-bone fractures (29%) compared with patients who did not receive indomethacin (7%; $p < 0.004$), strongly suggesting that long-term therapy with indomethacin clinically inhibited long-bone fracture healing.

In contrast, a prospective, randomised, double-blind, placebo-controlled clinical study did not find piroxicam to affect the healing of distal radial fractures in postmenopausal women despite treatment for eight weeks (51). Unfortunately, the outcome measures, data handling, and funding source for this study lead the reader to question the conclusion with regard to bone healing. The stated objective of this study was to determine whether piroxicam changed the degree of osteopenia in the nearby radius and ulna after coaptation for fracture, rather than whether piroxicam affected bone healing. The outcome measures were geared towards this objective, and included bone mineral content analysis of the radius and ulna *proximal to* the fracture site. Radiographic assessment of bone healing was limited to measurements of radial shortening and dorsal angulation of the radius over time. The piroxicam group had a statistically greater degree of dorsal angulation than the placebo group at four weeks but not at eight weeks. Of 42 patients, data from six fractures were omitted because excessive redislocation (defined by these authors as increased radial shortening and dorsal angulation) necessitated re-reduction and surgical external fixation; all six of these patients were in the piroxicam group. The authors justified the omission by pointing out that external fixation would have had an effect on the bone mineral content proximal to the fracture site.

Another prospective, double-blind, placebo-controlled study did not find that flurbiprofen, given for two weeks at various doses, had an effect on the healing of distal radial fractures (52). While bone area measurements in the hand (indices of osteoporosis), hand and wrist function, and pain were measured in the short term, fracture healing was not assessed until one year after fracture. If a transient delay in bone healing had occurred during flurbiprofen treatment, this study would not have detected it. However, this study is clinically helpful because it indicates that short-term use of flurbiprofen after distal radial fracture does not result in nonunion or significant malunion.

Retrospective observational studies have frequently found an association between NSAID use and increased nonunion rates after fracture or spinal fusion surgery in humans (▶Table 2). Few studies make an effort to identify confounding factors however, and their retrospective designs make inferences about causation difficult. For example, a large and frequently-cited retrospective study involving 9,995 patients with humeral shaft fractures reported a strong association between NSAID use and nonunion (53). Because this association was only significant in the latest time phase studied (61–90 days after fracture) and because the same pattern was observed with opioid use, the authors concluded that NSAID and opioid use were markers for patients in pain from unstable fractures, rather than the cause of nonunion.

Evidence in domestic species

Information about the effects of NSAID in domestic species is lacking. One publication suggests an effect on bone remodelling in horses and two studies address the effect on osteotomy healing in dogs (44, 54, 55).

An experimental study in horses found a decreased mineral apposition rate (a measure of Haversian remodelling) in bone adjacent to tibial biopsy sites in horses treated with phenylbutazone for two weeks (54). Although the healing biopsy sites contained less mineralised tissue at 16 and 30 days in phenylbutazone-treated horses than in control horses, this difference was not significant.

A prospective, randomised, placebo-controlled, cross-over study in dogs was performed to evaluate the effects of phenylbutazone and indomethacin on the postoperative course following experimental metacarpal osteotomy (55). Bone healing was evaluated by subjective assessment of radiographs taken two, four, six, and eight weeks after surgery. No attempt to objectively score the radiographs was reported, and whether this assessment was blinded was also not reported. In dogs treated with phenylbutazone the authors reported, "…radiographs taken four and six weeks after surgery … revealed tendencies in favour of placebo… After eight weeks, however, there were no noticeable differences." No noticeable radiographic differences in bone healing were seen in dogs treated with indomethacin. Given the lack of objective assessment and the fact that these two NSAID are rarely used in small animal medicine today, it is difficult to make clinical decisions based on this study.

Finally, a recent abstract described an experimental study designed to evaluate the effect of carprofen on bone healing in dogs (44). Healthy dogs received either carprofen (2.2 mg/kg PO q 12 hrs) or no treatment for four months after a tibial osteotomy was stabilised with an intramedullary pin. The NSAID group had delayed bone healing compared with the control group as detected by radiographical, biomechanical, and histological analysis.

Discussion

While NSAID negatively affect bone healing, there is insufficient evidence to support withholding NSAID after a fracture or orthopaedic procedure in domestic species. Certainly, fractures and osteotomies can heal in the face of NSAID administration, and NSAID are important for their potent anti-inflammatory and analgesic effects after bone injury. However, when the speed and effectiveness of bone healing is of particular concern, such as in delayed union, nonunion, tenuous orthopaedic repairs, or in patients where delayed bone healing is expected, it is prudent to consider the evidence when prescribing NSAID.

In rodent models, COX-2 selective NSAID do not seem to offer a benefit with regards to bone healing compared with nonselective NSAID. In humans, arguably the most convincing study showing a clinically relevant effect on bone healing involved indomethacin, a nonselective NSAID (50). In dogs, carprofen, a COX-2 selective NSAID, inhibited bone healing (44). The decision to use a COX-2 selective or nonselective NSAID should be made based on other criteria, such as the potential for adverse effects, cost, and availability.

Experimental literature suggests that higher doses and longer durations of NSAID are more detrimental to bone healing. In addition, there is evidence to support the notion that NSAID-induced inhibition can be reversible once the NSAID is discontinued. Reports that illustrate bone healing inhibition in humans and dogs involve NSAID administered for long durations (44, 50). Therefore, it makes sense to discontinue NSAID use after a reasonable post-injury period if the NSAID is no longer needed for analgesia.

Many other local and systemic factors can affect bone healing, making it difficult to isolate the independent effect of NSAID in a clinical setting. Local factors include type of fracture, fracture gap, fixation technique (reduction, position, stability), the presence of infection or debris, and the degree of vascularisation. Systemic factors include age and gender, metabolic and nutritional status, concurrent disease (endocrinopathies, neoplasia, immunodeficiency, chronic inflammatory disease, primary musculoskeletal disease), drug administration (corticosteroids, chemotherapeutic agents, antibiotics, anticoagulants, bisphosphanates, smoking), immobility, and others (56). The use of NSAID could have negative, additive, or synergistic effects on bone healing when combined with other conditions or environmental factors. To date there is little to no information investigating these combined effects or identifying patients at greatest risk for NSAID-induced delayed fracture healing.

Conclusion

Research using rodent and rabbit models provides strong evidence that NSAID negatively affect bone healing. Whether this effect is clinically important is controversial in both human and veterinary medicine. Prospective experimental and clinical trials involving domestic species and veterinary NSAID are needed to guide veterinarians as they decide which, when, at what dose, and for how long NSAID should be prescribed after bone injury.

Acknowledgements

I gratefully acknowledge Dr. Steve Martinez for his guidance and contribution to this manuscript.

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