J Musculoskelet Neuronal Interact 2009; 9(1):44-52

Review Article

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Do steroids, conventional non-steroidal anti-inflammatory drugs and selective Cox-2 inhibitors adversely affect fracture healing?

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide. They are prescribed for orthopaedic conditions such as osteoarthritis, soft-tissue injuries and fractures. The new generation of NSAIDs, selective cyclooxygenase-2 (COX-2) inhibitors, exhibit analgesic and anti-inflammatory effects equivalent or superior to conventional NSAIDs, while reducing the prevalence of adverse gastrointestinal events. Several reports from animal and *in vitro* studies have demonstrated impaired bone healing in the presence of conventional NSAIDs, as measured by a variety of different parameters. More recently, initial studies investigating the effects of selective COX-2 inhibitors on bone healing have yielded similar results, while other reports showed minor or no impairment of the healing process. The purpose of the present review article is the thorough review and analysis of the past 50-year literature and the attempt to get some conclusions about the effect of NSAIDs and selective COX-2 inhibitors on fracture healing and the clinical significance of their use in the management of postoperative and post-fracture pain.

Keywords: Fracture Healing, Steroids, Non-steroidal Anti-inflammatory Drugs, Selective COX-2 Inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide. They are prescribed for orthopaedic conditions such as osteoarthritis, soft-tissue injuries and fractures[1-5]. The new generation of NSAIDs, selective cyclooxygenase-2 (COX-2) inhibitors, exhibit analgesic and anti-inflammatory effects equivalent or superior to conventional NSAIDs, while reducing the prevalence of adverse gastrointestinal events[1-7].

Several reports from animal and *in vitro* studies have demonstrated impaired bone healing in the presence of conventional NSAIDs, as measured by a variety of different parameters[4,5,8-17]. More recently, initial studies investigating the effects of COX-2 selective inhibitors on bone healing have yielded similar results[5,15,18-21], while other reports showed minor or no impairment of the healing process[11,22,23]. An in-depth evaluation of the existing experimental studies shows that several variables such as dose, duration of administration and type of fracture healing influence the result. Moreover, experimental settings do not reflect the common clinical scenario of a patient who receives a low dose of an anti-inflammatory agent for a short duration.

Since the literature on this subject is inconclusive, this review paper attempts to give a thorough presentation of existing data and to reveal controversies and questions which have clinical significance.

General considerations

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide, with various indications in the management of several types of arthritis, menstruation pain, headaches and orthopaedic conditions such as soft-tissue injuries and fractures. Their use in fractures helps in controlling pain and swelling[8] and reduces the need for opioids. Conventional NSAIDs are

The authors have no conflict of interest.

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Accepted 11 December 2008

non-selective inhibitors of cyclooxygenase (COX) and inhibit equally both isoforms, COX-1 and COX-2. Therefore, they exhibit anti-inflammatory and analgesic effects through their action on COX-2, while their action on COX-1, which regulates several homeostatic physiologic functions of the gastrointestinal system and the kidneys, is responsible for possible side effects. The hypothesis behind the invention of the new generation of NSAIDs, the selective COX-2 inhibitors, was that they would have analgesic and anti-inflammatory effects equivalent or superior to conventional NSAIDs while reducing the prevalence of adverse side effects for the gastrointestinal system and the kidneys[24-28]. Meloxicam, a low selective anti-COX-2 agent, appeared first in 1995 and is now available in more than 100 countries. The first two coxibs, celecoxib and rofecoxib, were released into the US market in 1999. The invention and development of selective COX-2 inhibitors have further widened the indications of NSAIDs for diseases and injuries of the musculoskeletal system. Despite their indisputable contribution to the management of symptoms of bone injuries, clinical experience has raised questions regarding the effect of these drugs on fracture healing and the restoration of bone structural properties. There are several studies in the literature investigating the effect of NSAIDs on fracture healing, using different experimental protocols and various agents[1-5,9-32]. Despite some controversial results, there is strong evidence that steroids and conventional NSAIDs impair bone healing, prolong healing time and the restoration of the mechanical properties of bone, such as strength, while causing deterioration in the quality of the newly formed bone[8]. It is thought that these negative effects of NSAIDs are due to their anti-prostaglandin action. The prolonging of bone healing time is likely to be due to direct action on osteoblasts, inhibition of PGE_2 which stimulates osteoclasts, inhibition of pro-osteoblastic transformation[33] and stimulation and migration of neutrophils as well as phagocytosis[8].

Animal data suggest that the effects of COX-2 inhibitors on bone healing are probably both dose-dependent and reversible[1,3]. Since quality data from human studies does not exist, the topic is open to an in-depth critical evaluation.

NSAIDs and selective COX inhibition

NSAIDs are categorised by their selectivity in inhibiting the two isoforms of COX. The selectivity of each drug for either of the isoforms of COX is usually evaluated by the activity of each isoform in whole blood assays. These assays are based on the production of thromboxane B_2 during the formation of blood clotting (index of the activity of COX-1 on platelets) and the production of prostaglandin PGE_2 by bacterial lipopolysaccharide in whole blood (index of the activity of COX-2 on monocytes)[34-45]. Although the predictive value of these *in vitro* assays for evaluating the drugs' action *in vivo* has been questioned, they provide a relative measure of drug selectivity on COX-2. By determining the drug concentration needed to inhibit COX-1 and COX-2 by 50% (IC_{50}) and by calculating the COX-1/COX-2 IC_{50} ratio, we can compare the selectivity of each drug in COX-2 inhibition (Table 1)[32].

Substance	COX-1/COX-2 IC_{50} ratio
Traditional NSAIDs	
Fenoprofen	≤1
Ibuprofen	≤1
Indomethacin	≤1
Ketoprofen	≤1
Ketorolac	≤1
Naproxen	≤1
Paracetamol	≤1
Piroxicam	≤1
Aspirin	≤1
Selective COX-2 inhibitors	
Etodolac	5
Meloxicam	6
Diclofenac	12
Celecoxib	17
Nimesulide	23
Valdecoxib	44
Parecoxib	44
Rofecoxib	137
Etoricoxib	225

Table 1. COX-2 selectivity of several NSAIDs as assessed by whole blood assays[32]. COX-1/COX-2 IC_{50} ratio refers to the ratio between the drug concentrations required to inhibit the activity of COX-1 and COX-2 by 50%. Values are averages of reported ratios[34-36,41-45]. The higher the COX-1/COX-2 IC_{50} ratio, the higher the selectivity for COX-2 is.

The effect of steroids on fracture healing

It has been shown that the systematic long-term administration of prednisolone caused a definite inhibition of fracture healing in an experimental model of ulnar osteotomy in rabbits[46]. In this study 0.15 mg/kg/day of subcutaneous prednisolone was first administered to rabbits for 2 months, then an osteotomy was performed at the diaphysis of the ulna and prednisolone administration was continued for another 6 weeks, until the animals were sacrificed. The ulnae specimens were then studied radiologically and mechanically and more than 50% inhibition of fracture healing was reported in the treated animals compared to the controls. These results confirmed those of older studies in which steroid administration impaired fracture healing in rabbits[47,48]. Similar negative results were reported in a study in which the effect of dexamethasone (0.05mg/Kg intramuscularly twice per day) on experimental fusions in rabbits was evaluated[49]. In this study a decreased incorporation of bone grafts and an increased ratio of non-unions were reported. In contrast, in another study[13] no statistically significant differences were

observed when comparing the mechanical strength of healed rat femurs to controls, 6 weeks after osteotomy, and after short-term administration of methylprednisolone (0.20 mg/100 gr/day im for 3 days following osteotomy).

The effect of conventional NSAIDs on fracture healing

In most studies investigating the effect of NSAIDs on fracture healing, older conventional anti-inflammatory drugs have been used.

Indomethacin is the most studied NSAID. It has been administered in a dose of 2 mg/kg/day *per os* to a group of mice that had previously been subjected to closed fractures of the mid-diaphysis of the femur[33]. Impairment of fracture healing and mechanical properties, radiological instability and increase of angulation of the fractured femur with a delay in ossification of callus were observed in the indomethacin group[33]. In another study, the effect of indomethacin (1 mg/kg/day *per os*) and ibuprofen (30 mg/kg/day *per os*), administered for 4 and 12 weeks, on fracture healing in mice was also examined[8]. Mechanical tests and histological measurements showed a delay in fracture healing and decreased bone strength in all groups compared to the controls[8]. Keller confirmed these results by administering 10 mg/kg/day indomethacin, *per os*, to rabbits with tibial osteotomies[50]. A reduction of blood flow at the osteotomy area, a diminished mineralization of callus and a delay in bone remodelling were observed compared to controls. The effects of short-term (7 days) and long-term (28 days) administration of indomethacin (2 mg/kg/day *per os*) were investigated in mice with closed femoral fractures[51-54]. Impairment of fracture healing in both groups was shown. Bo and Allen confirmed these results[33,55]. In the latter study the inhibitory effect of aspirin on fracture healing was also demonstrated. Administration of indomethacin also had a negative effect on bone healing in a study performed by Hogevold[13], in which 0.20 mg/100 gr/day of indomethacin was orally administered to Wistar rats that had had a complete osteotomy on the mid-shaft of the femur. Indomethacin inhibited fracture healing either after having been administered for a short period (0.20 mg/100 gr/day orally for 3 days) or for a long one (same dose for 6 weeks)[13]. Indomethacin inhibits fracture healing even when locally administered at the fracture area[10]. Indomethacin was orally administered to a group of rats with stabilised femoral fractures (2 mg/kg/day for 10 days) and locally administered (0.5 mg once) to another group with similar fractures and fixation[10]. Increased mobility and angulation at the fracture site and delayed radiological healing were observed in both groups. The inhibitory effects of indomethacin (3 mg/kg/day for 12 weeks) have been demonstrated in rats on which experimental fusions were performed[56]. Riew reported similar results in rabbits on which experimental posterior fusion was performed[57]. In the latter study, the earlier the postoperative administration of indomethacin (10 mg/kg/day orally) was given, the stronger the inhibitory effect was.

Bhandari added either indomethacin or antibodies to IGF I and IGF II to cultures of bone cells taken from 7-day-old callus of fractured, reamed and stabilized mouse femurs[58]. Histological evaluation revealed an inhibitory effect of indomethacin, anti-IGF I and anti-IGF II in the early stages of bone healing. Ho also showed, in osteoblast cultures, that ketorolac and indomethacin impaired both osteoblast proliferation and mineralization of demineralized bone matrix grafts[59,60]. The same inhibitory effect has been shown with the administration of prostaglandins PGE_1 and PGE_2, a fact that leads to the conclusion that the negative effect of NSAIDs in fracture healing may not correlate with the inhibition of prostaglandin production. Boiskin measured Ca, osteocalcin and $1,25(OH)_2D$ vitamin in rats after administration of indomethacin (2 mg/kg/day sub cut) for 4 and 8 weeks, and found no significant differences in the histomorphometric parameters of bone formation or in cartilage histology compared to controls[61]. On the other hand, retardation of fracture healing caused by indomethacin could potentially prove to be an advantage in cases of physeal growth plate injuries. Indomethacin administration (10 mg/kg/day sub cut for 6 weeks) in juvenile rabbits with oblique osteotomies performed at the medial distal femoral condyle led to less angulation and better development of the cartilage compared to controls[62].

The administration of 30 mg/kg/day ibuprofen *per os* for 12 weeks (starting on the third post-operative day) in mice with fractured femurs failed to show significant differences in mechanical properties of the healed bone compared to controls[14]. No differences were observed, either in the histological picture of the callus or in the levels of serum osteocalcin and the histomorphometrical parameters of bone remodelling. At 3 weeks, Tornknist observed a reduction of the callus mass but no alteration in its composition in the ibuprofen treated rats with fractured femurs[16]. In this study, bone mass was restored at 9 weeks. Lebwohn reported an inhibitory healing effect of ibuprofen in rabbits with fusions[63]. This observation was not confirmed in a study conducted by Martin[64]. In the latter study, an increase in nonunion rates of the fusions was reported in ketorolac-treated animals[64]. Interestingly, the negative effect of ketorolac was inhibited by the co-administration of recombinant BMP-2.

The effect of tenoxicam in closed tibial fractures in rats has been investigated[12]. A dose of 10 mg/kg/day im tenoxicam of varying duration was administered to rats on which experimental fractures had been performed. Specimens showed, both histologically and histomorphometrically, delayed callus formation, which was greater the sooner the drug administration started.

Ketorolac (1 mg/kg/day im for 3 days), a low selectivity COX-2 inhibitor, and indomethacin (2 mg/kg/day for 3 days) were administered to rats with stable and unstable femoral fractures[65]. Ketorolac did not affect healing of unstable fractures, while indomethacin showed significant differences. Neither of the two drugs showed any inhibitory effect on stable fractures.

The effect of long-term administration of piroxicam (0.2 mg/kg/8 hours orally) was evaluated by More and Moed[66,67]. Piroxicam at this dosage did not inhibit fracture healing nor did it reduce heterotopic ossification. In contrast, in the same studies, indomethacin (10 mg/kg/day) inhibited both heterotopic and normal bone formation.

The effect of selective COX-2 inhibitors on fracture healing

Initial studies evaluating the effect of selective COX-2 inhibitors on fracture healing resulted in unclear and controversial messages.

Diclofenac (5 mg/kg/day for 7 or 21 days) was given orally to mice with experimental tibial osteotomies[9]. At 3 weeks, definite histological healing impairment and reduced callus mechanical properties was apparent in both groups compared to controls.

Etodolac (20 mg/day intraperitoneally) was given for 3 weeks to rats with undisplaced femoral fractures[18]. A statistically significant radiological delay of fracture healing and reduced callus strength and stiffness was observed in the etodolac group. In a recent study[68], the same group showed that the inhibitory effect of etodolac is stonger the sooner its post-fracture administration starts.

The effect of 4 weeks' administration of naproxen (110 mg/kg/day orally) and rofecoxib (12.5 mg/day orally) was studied in rabbits with tibial fractures[69]. A statistically significant reduction of both the callus volume and the number of osteoblasts in both groups compared to the controls was reported. More recently, the same group showed that the inhibitory effect of rofecoxib is proportional to the duration of its administration[70].

The effect of long-term administration (8 weeks) of indomethacin (1 mg/kg/day), celecoxib (4 mg/kg/day) and rofecoxib (3 mg/kg/day) in rats with experimental femoral fractures has been investigated[19,71]. It has been reported that celecoxib and indomethacin delayed but did not inhibit fracture healing while rofecoxib had a more definite inhibitory effect. Moreover, in the same study, genetically mutated COX-2 null mice exhibited severe inhibition of fracture healing compared to normal mice and COX-1 null mice. These results were confirmed by Zhang in experiments with genetically mutated COX-$2^{-/-}$ mice[21]. The above studies stress the important role of COX-2 in the process of fracture healing and especially in the recruitment of mesenchymal cells, stimulation of angiogenesis, normal endochondral ossification and callus formation. The effect of the administration of high doses of rofecoxib (8 mg/kg) and ibuprofen (30 mg/kg) on fracture healing has also been studied[15]. Rofecoxib delayed fracture healing and this inhibitory effect was even greater than that of ibuprofen. The above findings were also confirmed by Safanda et al[72].

The effect of selective COX-2 inhibitors on the healing of spinal fusions is as yet unclear. In an experimental study of spinal fusions in rabbits, celecoxib administration (10 mg/kg/day orally for 8 weeks) showed neither radiological nor histological delay in healing nor increase of non-union ratio[73]. In the same study, indomethacin (10 mg/kg/day orally for 8 weeks) showed a significant inhibitory effect. In a prospective, randomized, double-blind human study[74], no increase in the rate of spinal posterior fusion non-unions was observed after the administration of 400 mg of celecoxib orally for 5 days post-operatively. In a retrospective spinal fusion human study[75], the administration of celecoxib (600 mg/day orally), rofecoxib (50 mg/day orally) and low doses of ketorolac (<110 mg/day orally) for 5 days post-operatively, did not show any differences in fusion healing rates compared to controls. In contrast, high doses of ketorolac (240 mg/day orally) showed an inhibitory effect. High doses of ketorolac (180-240 mg/day) also demonstrated an increased non-union rate in a retrospective study in human spinal fusions[76].

The differential effect of ketorolac (4 mg/kg/day orally for 42 days) and parecoxib (doses of 0.3 and 1.5 mg/kg/day orally for 42 days), a highly selective COX-2 inhibitor, on healing of femoral fractures in rats has been investigated[11]. While ketorolac delayed fracture healing, parecoxib had a mild inhibitory effect at early stages of fracture healing only.

In another study, celecoxib (3 mg/kg/day for 8 weeks) showed no histological effect in the healing of femoral fractures in rats and the mechanical properties of callus were similar to controls[22]. In contrast, in the same study, indomethacin exhibited a clear inhibitory effect.

The effect of ibuprofen, ketorolac, celecoxib and rofecoxib on fracture healing in rats was evaluated and the conclusion that none of the four drugs is associated with a high ratio of non-union has been reported[23]. In contrast, the administration of celecoxib in dosages of 3 and 6 mg/kg orally for 10 days, in rats with closed diaphyseal femoral fractures, resulted in a delay in fracture healing and mal-union[77]. In the same study, the administration of high doses of paracetamol (60 and 300 mg/kg orally) for the same time period, demonstrated no inhibitory effect on healing.

The negative effect of diclofenac in alveolar wound healing after tooth extraction in rats has been reported[78]. Diclofenac (10 mg/kg/day intraperitoneally) significantly delayed new bone formation and impaired blood clot organization. The effect of rofecoxib (25 mg/day for 14 days) on the healing of intrabony periodontal defects in humans who were treated with an enamel matrix protein derivative has also been shown[79]. In the same study, an inhibitory effect of rofecoxib on bone defect healing has not been proven.

Critical analysis of literature data

The literature data definitely shows that steroid administration in the early stages of fracture healing delays the process[46-49]. Steroid administration causes decreased osteoblastic activity and therefore decreased matrix synthesis[80-82]. It had been shown that steroids also reduce the synthesis of type I collagen and osteocalcin mRNA. Type I collagen is the most abundant

bone matrix protein and osteocalcin is a highly specific marker of osteoblast lineage[83]. In addition, corticosteroids have been shown to alter transcription of alkaline phosphatase, bone sialoprotein, fibronectin, β1-integrin and interstitial collegenase mRNAs[83]. Steroids also diminish the production and activity of growth factors that are important for fracture healing and especially IGF-I and TGF-β[83]. Finally, corticosteroids negatively affect vitamin D metabolism and Ca absorption, decrease secretion of sex steroids due to adrenal suppression and possibly cause secondary hyperparathyroidism[84,85].

Indomethacin is one of the first conventional NSAIDs extensively studied in regard to fracture healing. In almost all studies, indomethacin showed an inhibitory effect on fracture healing[8,10,13,22,33,50-53,55-57,60,65-67,71,73]. Similar inhibitory effects were also reported for other conventional NSAIDs, like ibuprofen[8,58,59,61,62], ketorolac[11,23,75,76] and tenoxicam[12]. It is therefore clear that conventional NSAIDs have an inhibitory effect on bone healing whether their administration is short or long-term.

In the last 4 years the possible inhibitory effect of selective COX-2 inhibitors on fracture healing has been addressed. The literature data is inconclusive and occasionally controversial. There are studies in which COX-2 inhibitors demonstrate a negative effect on fracture healing[15,18,19,69-71,77], while in others no significant inhibitory effect has been reported[11,22,23,73-75,79,86].

There are two serious confounding factors in the published studies that we must pay attention to and comment on; the duration of administration and the dosage of the agents used. In the majority of studies, NSAIDs were administered in high doses and for a long period of time. However, the clinically relevant scenario for Orthopaedic Surgeons is of a patient who has sustained an injury or a fracture and who requires analgesia for a short period of time and takes low therapeutic doses. In a recent experimental study on rabbits, the short-term administration of low therapeutic doses of a selective anti-COX-2 agent resulted in a minor and reversible inhibitory effect on fracture healing while corticosteroids, indomethacin and a low selectivity anti-COX-2 agent administered in a similar way caused a prolonged inhibitory effect[86]. Another important issue is that the agents used in the studies may have different inhibitory concentrations of the two isoforms of COX in animals compared to humans. To the best of our knowledge, there is no data available concerning the level of COX-1 and/or COX-2 inhibition at the callus site of animals administered with different doses of NSAIDs. Moreover, there are no references concerning the precise pharmacokinetics of each agent in animals and therefore it is not possible to estimate the exact dose and the method of administration required to equally inhibit COX-1 and COX-2.

There are only 4 studies (3 in humans and 1 in animals) in the literature evaluating the short-term administration of selective COX-2 inhibitors. In two recent studies, Reuben studied the effect of celecoxib (400-600 mg/day for 5 days) and rofecoxib (50 mg/day for 5 days) in patients with posterior fusions and they reported no significant impairment of healing[74,75]. In another study Sculean investigated the effect of rofecoxib (25 mg/day for 14 days) on the healing of intrabony periodontal defects in humans who were treated with an enamel matrix protein derivative and found no inhibitory effect[79]. In an experimental study, Bergenstock observed an inhibitory effect of celecoxib after short-term administration (3 and 6 mg/kg for 10 days) in rats with diaphyseal femoral fractures[77]. It seems that the short-term administration of NSAIDs delays fracture healing but does not inhibit it and that this effect is both dose-dependent and reversible. It also seems that the effect of NSAIDs is stronger in the early stages of fracture healing, the inflammatory and haematoma stage, and that as soon as NSAIDs administration is discontinued, the normal process of healing is restored and the initially adverse effects are reversed[3,9]. This suggestion is supported by the study by Gerstenfeld who administered parecoxib to rats with femoral fractures and, although a mild impairment of healing was observed in the early stages, no significant difference was reported at 6 weeks post-fracture[11].

The results vary according to the selective COX-2 inhibitor used in every study[22]. In the authors' recent study it has been shown that the more selective the COX-2 inhibitors, the milder the impairment of fracture healing[86]. It seems that prostaglandins (PGs) produced in the fracture area are essential for the normal progress of healing. What remains unclear is whether their production is controlled by COX-2 exclusively or if local production of COX-1 is also important. It has been suggested that COX-1 takes part in the complex biochemical pathways of PGs production in the fracture area, protecting bone healing[11,73,87,88]. Several studies stress the important role of COX-1 in the processes of inflammation[7]. Other studies suggest that selective COX-2 inhibitors modulate the immunosuppressive effects of trauma and that this may have beneficial effects on tissue healing[11,89,90]. It is therefore possible that systemic and local alterations in the selective production of prostaglandins by COX-1 and COX-2 may lead to differing biological responses, which could affect local tissue repair[11].

Different experimental animal models show varied and controversial results[88]. It is possible that healing is affected by secondary factors related to each agent and not only by the direct action of the agent, for example, the level of analgesia each drug offers and the various degrees of weight-bearing this analgesia allows the animals. Genetically mutated COX-2 knockout animals were used in two studies[19,21], and significant impairment of fracture healing was observed in these animals. However, great attention must be paid when we attempt to compare animals in which COX-2 has been inhibited genetically to animals with pharmacologic inhibition of COX-2. Such comparisons are unsafe since, even in the study performed by Simon[19], it is clear that there are quantitatively measurable differences in the effects of various selective and non selective inhibitors of COX-2 on fracture healing. Thus, there may be variations in how different pharmacological agents act locally or at the end

organs on which they act when they metabolise[11].

Despite a significant number of animal studies on the effect of NSAIDs on bone healing, and several valid studies demonstrating that NSAIDs protect from heterotopic ossification after a total hip replacement or a pelvic fracture in humans[1,30,91,92], there are not enough valid studies on humans. To the best of our knowledge only four studies on humans have been published[74,75,79,91], and yet only one of them concerned fractures. In the first study, rofecoxib did not impair the healing of intra-bony periodontal defects. In the other two studies, no inhibitory effect of short-term administration of celecoxib, rofecoxib and low doses of ketorolac on human fusions was observed, while high doses of ketorolac inhibited healing. The only existing retrospective study in humans suggests a marked association of non-union with NSAID use in patients with femoral shaft fracture[91]. The possibility of administering anti-COX-2 agents to patients with fractures must be addressed in randomized human clinical trials. However, in our opinion, this will be difficult because of ethical issues and difficulties in patient recruitment to a study which tests the ability of a drug to inhibit healing, because of recent concerns regarding cardiovascular toxicity and owing to difficulties in the grouping of individual fracture patterns, assessing healing and identification of end points.

Until such data is available, the role of COX-2 in human fracture healing should be drafted from basic science studies in animals[3,86].

A concise view on the interaction between NSAIDs and PGs

NSAIDs interfere with the production of certain types of prostaglandins (PGs), a form of eicosanoid, which have various effects on blood vessels, nerve endings and cells involved in the inflammatory cascade[4,93]. Eicosanoid synthesis begins with the release of arachidonate from the membrane phospholipids via the activity of phospholopase A_2 (PLA_2). Subsequently, two different cyclooxygenase (COX) isozymes convert arachidonic acid into various PGs[93]. It is at this point that NSAIDs, by interfering with the activity of COX enzymes, inhibit the production of PGs[94,95,96]. Although closely related, the COX enzymes differ in certain important repects. COX-1 functions as a constitutive enzyme located in a wide range of various tissue types such as the gastric mucosa, kidneys and intestine. At these sites, the enzymes produced by COX-1 PGs are necessary for normal cell activity but do not appear to play a role in the inflammatory process[93]. Conversely, COX-2 is an inducible enzyme that operates as "an immediate early response gene product in inflammatory and immune cells"[93]. At the sites of injury and inflammation, macrophages, fibroblasts and synovial cells release COX-2, which subsequently up-regulates the production of PGs, especially PGE_2, involved in the inflammatory response[95,96]. When a fracture occurs, the local blood flow in the area is disrupted leading to the death of cells in the area. The resorption of these necrotic tissues causes an aseptic inflammatory response and a massive production of prostaglandins, which consequently trigger the proliferation and differentiation of pluripotent osteoprogenitor cells, ultimately leading to new bone matrices[97]. The locally released prostaglandins also increase the activity of osteoblasts and osteoclasts, all of which are ultimately essential to proper bone healing[98]. Traditional NSAIDs inhibit the activity of COX-1 as much or more than COX-2. Thus, NSAIDs inhibit the production of PGs at the site of the fracture and thereby impair the proper flow of the entire bone healing cascade. The exact roles of COX-1 and COX-2 in the PGs production are not yet clear; thus assumptions can be made about a milder inhibitory effect of selective COX-2 inhibitors on bone healing, compared to traditional NSAIDs.

Conclusions

NSAIDs and especially selective COX-2 inhibitors are important in the management of post-operative and post-fracture pain and lead to considerable reduction of opioid needs. Steroids and older non-selective anti-COX-2 agents adversely affect, to a varying degree, fracture healing. Concerning modern selective anti-COX-2 agents the literature is inconclusive, with their action on fracture healing probably being time- and dose-dependent. Clinicians must be aware of all previously mentioned data, in making decisions. In the authors' opinion, when NSAIDs are used after a fracture as an analgesic, selective COX-2 inhibitors should be preferred as long as the duration is short-term, possibly no more than 10 days. At least in theory, these inhibitors must be avoided in patients who smoke, take corticosteroids, suffer from diabetes or if the fracture shows signs of delayed or non-union.

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