CHAPTER **5**

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND BONE HEALING

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Nonsteroidal anti-inflammatory drugs (NSAIDS) are among the most widely prescribed medications today. An estimated 17 million people take these drugs daily, with approximately 60 million prescriptions written by physicians each year.[1] These medications are used to treat a wide variety of musculoskeletal disorders, including osteoarthritis and rheumatoid arthritis. Because NSAIDS have anti-pyretic, analgesic, and anti-inflammatory properties, they provide a non-habit forming, steady state background for pain control, reducing the need for narcotics. As a result, NSAIDS have become a popular choice for pain control in the postoperative setting. In addition, using NSAIDS throughout the peri-operative period has been shown to decrease the need for post-operative narcotics.[2]

CYCLOOXYGENASE PATHWAY

Conventional NSAIDS work by inhibiting the production of prostaglandins (Figure 1). Two enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), catalyze the production of prostaglandins from arachiodonic acid. These prostaglandins stimulate numerous regulatory functions and reactionary responses throughout the body, including the inflammatory process. COX-1 is a constitutive enzyme that produces "house keeping" prostaglandins responsible for the production of gastric mucous, kidney water excretion, and platelet formation. COX-2 is an inducible enzyme that produces prostaglandins responsible for the inflammatory response.[3]

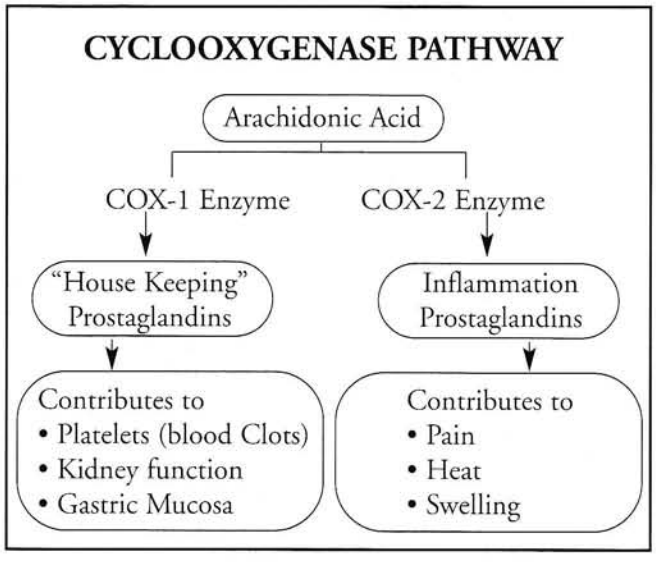

Figure 1. Cyclooxygenase Pathway.

There are two general categories of NSAIDS: non-specific COX-1 and COX-2 inhibitors and specific COX-2 inhibitors. Non-specific COX-1 and COX-2 inhibitors include NSAIDS such as Motrin (ibuprofen), naproxen (naprosyn), Indocin (indomethocin). Specific COX-2 inhibitors include medications such as Celebrex (celecoxib), Vioxx (valecoxib), and Bextra (valdecoxib).

Because prostaglandins play a key role in numerous processes throughout the body, inhibition of prostaglandin production via NSAIDS produces both desirable benefits and undesirable side effects. These side effects have been well documented and include gastrointestinal irritation, anemia, and disturbance of platelet function.[4] The incidence of side effects, namely GI irritation, has been reduced with the advent of COX-2 specific inhibitors, which target only the inflammatory prostaglandins.

Recent evidence suggests that one of the processes influenced by prostaglandins is bone healing. As a result, numerous authors have recommended avoiding the post-operative use of NSAIDS in cases of elective osseous procedures and/or fracture repair.[4-6] This paper will examine the evidence from laboratory, animal and human studies, and make recommendations for the use of NSAIDS following elective osseous surgery and fracture repair.

BONE HEALING

To understand the effects of NSAIDS on bone healing, a review of the basic process of bone healing is required. There are three stages in bone healing: 1) inflammation stage, 2) repair stage, and 3) remodeling stage. During the inflammatory stage, a hematoma develops within the fracture site. At this time, prostaglandins are activated that mediate the invasion of inflammatory cells (macrophages, monocytes, lymphocytes, and polymorphonuclear cells), and fibroblasts into the fracture site. This results in the

formation of granulation tissue, ingrowth of vascular tissue, and migration of mesenchymal cells. This stage lasts approximately 1-7 days.

The repair stage occurs approximately 2-4 weeks. During this stage, fibroblasts lay down stroma that assists in vascular ingrowth. A collagen matrix is laid down while osteoid is secreted, leading to the formation of a soft callus around the fracture site.

The final stage, the remodeling stage, can last from 6 weeks to a year. At this time, the bone remodels according to the mechanical stresses placed upon it.[7]

NSAIDS AND BONE HEALING

Nonsteroidal anti-inflammatory drugs have been demonstrated to inhibit bone metabolism in animal models, likely via reduced prostaglandin synthesis. In animal studies, it was found that prostaglandins were released after a fracture and throughout the inflammatory phase of bone healing.[8] In another study, these prostaglandins were shown to stimulate bone formation and resorption.[9]

In addition, animal studies have shown that the quality of bone formed during administration of NSAIDS is histologically and biomechanically inferior.[10] Atlman et al found that indomethacin and ibuprofen treatment for 10 weeks postfracture, delayed the maturation of callus and retarded femoral fracture healing in rats.[11]

Giannoudis et al performed a respective study comparing 377 patients treated by intramedullary nailing for fractures of the shaft of the femur. They assessed many risk factors potentially affecting fusion such as smoking habit, sex, age, and the use of NSAIDS. They found a statistically significant association ($P < 0.000001$) between delayed unions and nonunions and the use of NSAIDS. This effect was greater than the negative effect of smoking.[12]

Glassman et al performed a retrospective review of 288 spinal fusions and compared the nonunion rates between patients who were administered a loading dose of 60 mg IM Ketorolac followed by 30 mg IM every 6 hours as needed (167 patients) versus patients who were given a placebo (121 patients). Nonunion occurred in 17% (29/167) of those receiving Ketorolac and only 4% (5/121) of patients taking the placebo, a statistically significant difference ($P < 0.001$) with an odds ratio of 4.9 (1.8 to 1.7). There was also a dose-dependent relationship between nonunion rates and the dose of Ketorolac.[13]

In another study, Burd et al performed a retrospective review of 112 patients with long-bone fractures and compared the nonunion rates between patients who were administered oral indomethicin 25 mg TID for six weeks with those receiving placebo. Nonunion occurred in 29% (11/72) of patients receiving indomethacin and 7% (5/118) of patients receiving placebo. The difference was statistically significant ($P < 0.004$) and the odds ratio for developing a nonunion was 5.32 to 1.[14]

Since the development of specific COX-2 NSAIDs, research has been performed to investigate whether the effects of NSAIDS on bone metabolism are due to the COX-1 enzyme or COX-2 enzyme. Recent evidence suggests that bone healing is more COX-2 mediated. Simon et al showed that during the inflammation stage, COX-2 enzymes were induced. They studied the rate of nonunions and mechanical properties of the fracture callus in mice treated with indomethacin or celecoxib or rofecoxib. They found that after 8 weeks, mice treated with the COX-2 NSAID had a higher nonunion rate and weaker mechanical properties than mice treated with indomethacin.[15] Goodman et al compared bone ingrowth and tissue differentiation in vivo between rats treated with naprosyn and rofecoxib. They determined that NSAIDS containing a COX-2 inhibitor suppressed bone in-growth. Therefore, treatment with COX-2 specific inhibitors will prevent delays in bone healing.[16]

POSTOPERATIVE RESUMPTION OF NSAIDS

Is there a proper time to resume nonsteroidal anti-inflammatory postoperatively? Many patients rely on anti-inflammatory medications to treat their musculoskeletal ailments. In addition, the use of nonsteroidal anti-inflammatory drugs can reduce the use of narcotics. A study by Riew et al, studied the minimum amount of time to delay initiation of postoperative NSAIDS necessary to decrease the known effects on bony fusions. They performed spinal fusions on rabbits and divided them into three groups: groups 1 and 2 received oral indomethacin two weeks and four weeks postoperatively, respectively. Group 3 was given saline tablets as a placebo. At six weeks postoperatively, the rabbits were sacrificed and the spinal fusion was analyzed for fusion. Fusion was defined as no motion at the fusion site with manual pressure. Group 1 had a fusion rate of 21%, group 2, 48%, and group 3, 65%. The difference between group 1 (2 week post-operative) and group 3 (control) was statistically significant ($P < 0.002$) and between group 2 (4 week post-operative) and group 3 was not statistically significant, indicating that after 4 weeks the effect of NSAIDS on bone healing is indistinguishable from placebo. Since this study was performed with rabbits, the human equivalent of 4

weeks postoperatively is unknown. Hence, the authors of this study recommended postponing postoperative NSAID use as long as possible, especially in the early phase of bone healing.[17]

ALTERNATIVES TO NSAIDS

To avoid the potential complication of delayed or nonunions, other postoperative pain medications can be prescribed. Some non-narcotics that can be used are acetaminophen, tramadol, propoxyhene, and fioracet. These medications can provide effective postoperative analgesia without the potential side effects on bone healing.[18]

SUMMARY

To date, evidence in the literature suggests that NSAIDS have potentially deleterious effects on bone metabolism and fusions. However, there is yet to be a randomized, double-blind placebo-controlled trial in patients that specifically examines the effects of NSAIDS on bone fusions. Additionally, most of the studies have been performed in animals. Despite this, at this time, the use of NSAIDS should be avoided when bony fusion is desired postoperatively. If used, NSAIDS should be used in low doses and should be delayed postoperatively for a minimum of one week.

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