

The Role of Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Acute Soft Tissue Injuries

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Objective: Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to hasten the return of injured athletes to competition after injury. Evidence demonstrates that while NSAIDs may speed recovery after acute soft tissue injuries, long-term healing may be compromised. This review aims to assess the effects of NSAIDs on inflammation and healing associated with acute soft tissue injury.

Data Sources: CINAHL (1982 to 1997), SPORT Discus (1977 to 1997), and MEDLINE (1993 to 1997) were searched using the keywords "NSAIDs," "musculoskeletal," "acute," "sprain," and "strain."

Data Synthesis: NSAIDs exhibit anti-inflammatory effects via prostaglandin inhibition, neutrophil migration suppression, and oxygen free-radical inhibition. Retardation of inflammatory processes after acute injury may limit the area of secondary

tissue damage but may also retard healing. Animal models have demonstrated short-term benefits with NSAIDs after acute injury, along with long-term adverse effects on tissue structure and function. NSAIDs have exhibited few benefits in the treatment of delayed-onset muscle soreness. Clinical trials of NSAIDs in the treatment of acute soft tissue injuries have shown conflicting results and have been highly criticized.

Conclusions/Recommendations: Based on the research literature, the short-term benefits of NSAIDs in the treatment of acute soft tissue injuries must be weighed against the potential long-term adverse effects on tissue healing, structure, and function.

Key Words: NSAID, acute injury, delayed-onset muscle soreness, inflammation

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a family of drugs that have achieved widespread use in sports medicine in both prescription and over-the-counter (OTC) forms. NSAIDs are often administered after acute soft tissue injury in an effort to minimize pain and inflammation and thus hasten an injured athlete's return to competition. However, recent evidence suggests that the short-term benefits of NSAID therapy may adversely affect the long-term healing of injured soft tissues.¹⁻³ This article will examine the classification of NSAIDs, the acute inflammatory process, the mechanisms of action of NSAIDs, and the positive and negative effects of NSAIDs on soft tissue healing.

Aspirin (acetylsalicylic acid), originally derived from the bark of the willow tree, was the first NSAID and has been used in various forms to treat human ailments for centuries.^{4,5} Originally marketed in the United States by the Bayer Corporation in the late 1800s, aspirin was heralded as a panacea.⁵ However, the primary physiologic mechanism of action of aspirin was not discovered until 1971, when Vane⁶ reported that prostaglandin production was inhibited by aspirin. Numerous side effects associated with ingestion of aspirin led to the development of other chemically similar drugs, now known as NSAIDs, that have clinical properties similar to aspirin but fewer adverse side effects. NSAIDs are primarily administered for their analgesic, antipyretic, anti-inflammatory, and anticoagulant effects.

NSAIDs are most commonly administered orally and are broken down in the gastrointestinal system. The drug circulates and is metabolized by either the kidneys or the liver, depending

on the individual properties of the NSAID. NSAIDs may also be delivered via topical gels, phonophoresis, iontophoresis, or intramuscular injection, although the efficacy of these routes of administration is not as well studied as the oral route of administration. This article will concentrate on the properties of orally administered NSAIDs.

CLASSIFICATION OF NSAIDS

Three classification systems are used to describe NSAIDs. The first system distinguishes between prescription and OTC NSAIDs. Prescription NSAIDs must be prescribed by a health care provider licensed by the individual state and are more potent and, thus, also potentially more harmful than OTC NSAIDs. Dosages of prescription NSAIDs are much higher than those available OTC. NSAIDs are one of the most commonly prescribed classes of pharmaceuticals. In the past few years, many more OTC NSAIDs have become available in the United States (Table 1). Athletic trainers must be extremely cautious in the recommendation of OTC NSAIDs to athletes and must be aware of the drugs' characteristics.

OTC NSAIDs are available in doses that primarily yield analgesic and antipyretic effects, but not anti-inflammatory effects. The dosage to achieve anti-inflammatory effects generally is twice that needed to achieve analgesic effects.⁷ Clinically, it is very difficult to distinguish between the anti-inflammatory and analgesic effects of NSAIDs.⁸

Another means of classifying NSAIDs is by chemical structure (Table 2). If the desired effects from a given NSAID are not obtained after 2 weeks of consistent drug therapy, a trial with an NSAID from a different chemical classification is recommended.⁹

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Table 1. Over-the-Counter NSAIDs and Their Common Trade Names Available in the United States*

Active Drug	Common OTC Trade Names
Acetylsalicylic acid	Aspirin, Ascriptin, Bufferin, Excedrin
Ibuprofen	Motrin, Advil, Nuprin
Ketoprofen	Orudis KT, Actron
Magnesium salicylate	Doan's Analgesic
Naproxen sodium	Aleve

* Summarized from the *Physicians' Desk Reference for Nonprescription Drugs*.⁵¹

NSAIDs are also commonly classified by half-life (Table 3), the time necessary to eliminate half of the ingested amount of drug from the body.⁴ The half-lives of NSAIDs vary from less than an hour to more than 24 hours. Peak plasma concentrations and peak clinical effects are seen after 3 to 5 half-lives when the patient is consistently taking the medication.^{4,7,9,10} Drugs with short half-lives normally are taken three to six times per day to achieve anti-inflammatory effects. Peak plasma concentrations and peak clinical effects can be seen sooner with short half-life NSAIDs. In contrast, drugs with longer half-lives are taken only once or twice per day and are slower in eliciting the desired clinical effects. However, patients who are prescribed drugs with longer half-lives tend to be more compliant in taking their medication.¹⁰ It is interesting to note that all but one of the OTC NSAIDs (naproxen sodium) are in the short half-life category.

Acetaminophen is a drug that is not an NSAID but deserves special mention. Acetaminophen (commonly marketed as Tylenol) renders analgesic and antipyretic effects but not anti-inflammatory or anticoagulant effects. It appears to operate independently of the cyclooxygenase pathway by which

NSAIDs work. Acetaminophen is commonly administered for its analgesic effects after acute injury.⁵

THE INFLAMMATORY PROCESS

After acute injury, inflammation is the body's method of limiting the amount of tissue damage and protecting against further insult. Injury to soft tissue results in a nonspecific physiologic response that activates a series of proinflammatory events. Immediate vasoconstriction limits local hemorrhage and is followed by subsequent vasodilation and an increase in vascular permeability near the site of injury.¹¹ Platelets quickly adhere to one another at the site of capillary damage to provide a mechanical plug to prevent further bleeding. The clotting cascade is simultaneously activated and results in the formation of fibrin and fibronectin, which form cross-links with collagen to reinforce the temporary plug and stop hemorrhage.¹¹ The zone of primary injury is defined by the extent of the initial hematoma.¹⁰

Bradykinin, serotonin, and histamine are pain-producing chemical mediators that are released quickly after trauma and aid in the attraction of leukocytes to the site of injury. Table 4 summarizes the role of the different leukocytes in the inflammatory process.

Arachidonic acid is a phospholipid that is a component of all cell membranes. Injury causing disruption of a cell membrane allows an increase in intracellular Ca^{++} , leading to the activation of phospholipase A_2 , which cleaves arachidonic acid from the cell membrane. Arachidonic acid is then metabolized by either the cyclooxygenase or lipoxygenase pathways. Prostaglandins, thromboxanes, and prostacyclin are produced via the cyclooxygenase pathway, while leukotrienes are produced

Table 2. Chemical Classifications of Common NSAIDs and Their Common Trade Names*

Carboxylic Acids	Enolic Acids	Nonacids
Propionic Acids Carprofen (Rimadyl) Fenoprofen (Nalfon) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Ketoprofen (Orudis) Naproxen (Aleve, Naprosyn) Naproxen sodium (Anaprox) Oxaprosin (Daypro)	Oxicams Piroxicam (Feldene) Pyrazolones Oxyphenylbutazone Phenylbutazone (Azolid, Butazolidin) Pyrrrolopyrroles Ketorolac (Toradol)	Nabumetone (Relafen)
Fenamates Meclofenamate sodium (Meclomen) Mefenamic acid (Ponstel)		
Acetic Acids Diclofenac sodium (Voltaren) Etodolac (Lodine) Indomethacin (Indocin) Sulindac (Clinoril) Tolmetin (Tolectin)		
Salicylates Acetylsalicylic acid (Aspirin) Diflunisal (Dolobid) Salsalate (Salflex, Disalcid) Magnesium salicylate (Doan's Analgesic) Choline magnesium trisalicylate (Trilisate)		

* Summarized from various sources.^{4,5,7,9,23,52-54}

Table 3. Classification of NSAIDs by Half-Life*

Short Half-Life	(<6 h)	Long Half-Life	(>6 h)
Aspirin	.25-.33	Diflunisal	8-12
Diclofenac sodium	1-2	Choline magnesium trisalicylate	9-17
Magnesium salicylate	1-2	Naproxen sodium	12-13
Ibuprofen	1-2.5	Naproxen	12-15
Ketoprofen	1.6-4	Salsalate	3.5-16
Fenoprofen	2-3	Sulindac	16-18
Mefenamic acid	2-4	Piroxicam	24-38
Tolmetin	2-6	Nabumetone	24
Meclofenamate sodium	3-4	Oxaprozin	25
Indomethacin	4-5	Phenylbutazone	77
Flurbiprofen	4-6		
Ketorolac	4-6		
Etodolac	6-7		

* Summarized from various sources.^{4,5,7,9,23,52-54}

via the lipoxygenase pathway. The Figure illustrates the arachidonic acid cascade.

Prostaglandins, especially PGE₂, play an integral role in the inflammatory process and may be produced by all cells in the human body except erythrocytes.¹² They signal a plethora of proinflammatory events including induction of vasodilation, increased vascular permeability, increased local blood flow, and increased body temperature via actions on the hypothalamus. Prostaglandins also serve to increase the sensation of pain by decreasing the sensitivity of nociceptors and potentiating the effects of bradykinin and histamine.¹⁰ PGE₂ expression may increase 10- to 80-fold during acute inflammation.¹⁰ Additionally, PGE₂ attracts leukocytes to the site of inflammation.¹¹

Prostacyclin and thromboxane are chemically unstable, yet extremely potent, compounds that have antagonistic actions during inflammation.¹³ Prostacyclin, also known as PGI₂, inhibits platelet aggregation on blood vessel walls, while thromboxane A₂ induces rapid platelet aggregation and vasoconstriction.^{5,12} This antagonist relationship serves to control the amount of local bleeding that occurs after injury.

Leukotrienes are derived from arachidonic acid via the lipoxygenase pathway. Leukotriene B₄ (LKB₄) is an extremely potent chemoattractant for leukocytes and causes an increase in vascular permeability.^{12,14} LKB₄ can also stimulate granulocyte aggregation to the site of injury.¹⁵ Other leukotrienes are not as potent as LKB₄, but they do play an inflammatory role in slow-reacting anaphylaxis (for example, during asthma attacks).¹⁵

Neutrophils are the first leukocytes attracted to the site of inflammation by many of the previously discussed mediators. Neutrophil activation results in a respiratory burst, which is characterized by the generation of high concentrations of oxygen free radicals and reactive oxygen species such as hydrogen peroxide (H₂O₂), superoxide anions (O₂⁻), and hydroxyl radicals (HO·).^{14,16-18} These are extremely reactive and chemically unstable compounds that attack cell membranes and break down cell walls via the production of lysosomal enzymes such as collagenase.^{10,17} Lysis of cell membranes further potentiates the inflammatory process by

Table 4. Characteristics of Leukocytes Involved in the Acute Inflammatory Response*

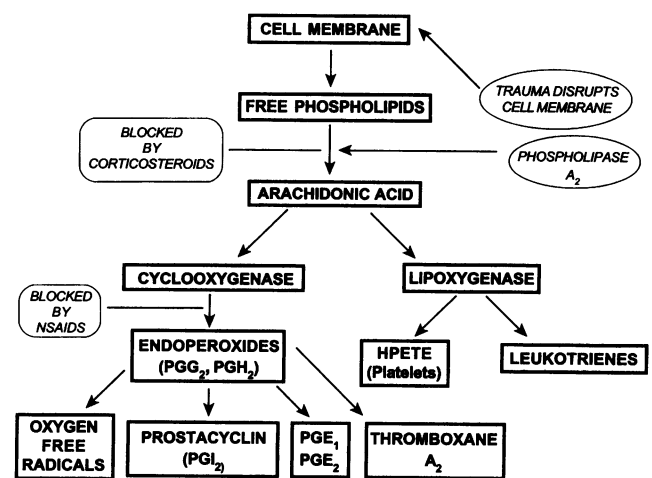
Leukocyte	Time to Response	Function
Neutrophils	3 minutes to a few hours	Phagocytosis of small debris Lysis of cell walls Generate oxygen free radicals Attract other leukocytes
Eosinophils	30 minutes to a few hours	Promote clotting Neutralize leukotrienes and histamine Phagocytosis
Basophils	2-6 hours	Anticoagulant effects Stimulate local edema Phagocytosis
Macrophages	24-48 hours	Phagocytosis of large debris
Lymphocytes	Hours to days	Immunologic functions

* Summarized from Reeves & Todd.⁵⁵

liberating additional amounts of arachidonic acid from cell membranes.

More cell damage can occur from the edema and tissue hypoxia that are the result of the acute vascular inflammatory response. This subsequent tissue damage is often referred to as the "secondary zone of injury," in contrast to the initial damage caused by the actual mechanism of injury.¹⁰

There are also other components of the inflammatory process, such as the complement system and a complex interaction of cellular messengers known as cytokines. The complement system provides a nonspecific reaction to injured tissue and infectious particles by assembling a membrane attack complex and attracting leukocytes to the site of injury.¹⁴ Several cytokines that are also known as interleukins have been identified as active components in chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis, but their exact role in the inflammatory process associated with acute soft tissue injury is not fully understood.^{14,19}

**The arachidonic acid cascade.**

Macrophages will migrate to the area of inflammation within 24 hours of initial trauma and begin to phagocytize necrotic debris. At this point, the inflammatory process becomes a healing process as the body begins to clear away damaged tissues and lay the foundation for new tissues. Rampant phagocytosis normally lasts for several days after injury but varies depending on the severity of the injury.¹¹ As phagocytosis is nearing completion, fibroblasts and granulocytes are drawn to the site of injury by growth factors, and new collagen is produced in an effort to replace the injured tissues. This is referred to as the proliferation phase of healing. A new network of capillaries is established within a few days of trauma to ensure that the scar tissue is well vascularized.¹¹

The tensile strength at the site of injury is at its weakest between day 2 and day 5 after injury.¹¹ Tensile strength is normally increasing by day 7 after injury and, as new tissue is constructed, the original scar tissue is being dissolved.¹¹ The scar eventually decreases in size, and tissue remodeling occurs according to the specific demands placed on the healing tissues. Complete scar maturation may take up to 1 year.¹¹

Effects of NSAIDs on Prostaglandin Synthesis

The primary mechanism of action of NSAIDs has been identified as inhibition of prostaglandin synthesis by blocking the cyclooxygenase pathway of the arachidonic acid cascade.⁶ By blocking the cyclooxygenase pathway, the production of prostaglandins, thromboxane, and prostacyclin are thus thwarted by NSAIDs. However, the inflammatory process is not stopped entirely by NSAIDs because the arachidonic acid cascade is able to continue via the lipoxygenase pathway.²⁰ LKB₄, an extremely potent inflammatory mediator, and other leukotrienes are still produced in the presence of NSAIDs.¹⁵

Two isoenzymes of cyclooxygenase have been identified and are referred to as cox-1 and cox-2.²¹ NSAIDs act indiscriminately on both cox-1 and cox-2. Cox-1 functions as a physiologic "housekeeper" and induces prostaglandin synthesis for normal healthy body functions, such as producing cytoprotective mucus in the digestive tract.²² Prostaglandins are required for normal physiologic processes to occur in the gastrointestinal tract, kidneys, liver, and other organs. When cox-1 is inhibited by NSAIDs, prostaglandin synthesis does not occur in the gastrointestinal tract, kidneys, and other organs, and, thus, the normal physiologic functions carried out by prostaglandins cannot occur. Inhibition of cox-1 causes many of the visceral side effects associated with NSAIDs.²²

Cox-2 is present in most tissues in small amounts, but levels are enhanced considerably at sites of inflammation.²² Cox-2 is involved in prostaglandin synthesis associated with the inflammatory process. NSAIDs blocking cox-2 thus inhibit prostaglandin synthesis associated with inflammation. Hence, the ultimate anti-inflammatory drug would theoretically inhibit prostaglandin synthesis mediated by cox-2 while having no effect on cox-1.²²

Nonprostaglandin Effects of NSAIDs

While NSAIDs are known to slow inflammation by blocking the cyclooxygenase pathway of the arachidonic acid cascade, NSAIDs also have anti-inflammatory effects unrelated to arachidonic acid. NSAIDs are known to inhibit neutrophil aggregation and migration to sites of inflammation.¹⁰ Other alterations of neutrophil function are also affected, including the slowing of lysosomal enzyme release, decreased oxidative phosphorylation, and decreased production of substances that are chemotactic for other leukocytes. Oxygen free-radical production by neutrophils and phagocytes is also decreased in the presence of NSAIDs.¹⁰

Anion transport across cell membranes has been shown to be diminished, while Ca⁺⁺ transport into cells is facilitated by NSAIDs.¹⁶ NSAIDs have also been shown to have anticoagulant effects by acting on platelets.¹⁶ NSAIDs may also inhibit T-cell activity and the release of histamine by mast cells.^{23,24}

Effects of NSAIDs on Muscle and Ligament Injury Models

Researchers utilizing animal models to study the histologic effects of NSAIDs on muscle and ligament injury have shown that NSAIDs yield short-term improvements in muscle healing and function, but either no long-term benefits or potentially deleterious long-term effects on muscle structure and function.¹⁻³

Mishra et al¹ induced muscle strain to the anterior tibialis muscle of rabbits, treated one group with flurbiprofen and another group with a placebo, and then assessed muscle function and histology at 3, 7, and 28 days after injury. The treatment group was able to generate greater peak torque and exhibit greater maximum tetanic tension than the placebo group at days 3 and 7 postinjury. However, at 28 days, those treated with flurbiprofen were able to produce less torque and demonstrated less maximum tetanic tension than those treated with the placebo. In addition, the treatment group had significantly less structural protein loss at the site of injury at 3 and 7 days postinjury and fewer circulating lymphocytes than the placebo group at 7 days.

In a study examining the effects of piroxicam on the healing and function of anterior tibialis muscle strains in rabbits, the piroxicam-treated group was able to generate more contractile force than the placebo group on the day after injury.² No significant differences were found in maximum tetanic contraction between the groups through 1 week postinjury. However, the piroxicam-treated group subjectively appeared to have delayed inflammation and healing compared with the placebo group throughout the first week after injury.²

The effects of immobilization and piroxicam with immobilization after stretch-induced muscle injury to the anterior tibialis muscle of rats were compared at 0, 2, 4, and 11 days after injury.³ The piroxicam-treated group exhibited greater maximum tetanic tension than the immobilization group at days 2 and 11. The piroxicam-treated group also had less macrophage invasion at day 2. In addition, the immobilization

group had more subjective signs of healing than the piroxicam group at day 11.³

Thomas et al²⁵ studied the effects of indomethacin on the healing of Achilles tendon ruptures in rabbits and found no differences in tensile strength or histologic examination up to 6 weeks after the injury. The results of this study demonstrating no effect of indomethacin on soft tissue healing are in contrast to studies that have shown indomethacin to retard the healing of fractures.^{26,27}

Almekinders et al¹⁹ examined the *in vitro* effects of indomethacin on DNA synthesis, protein synthesis, and PGE₂, LKB₄, and interleukin-6 levels in human tendon fibroblasts exposed to bouts of repetitive motion over the course of 108 hours. PGE₂ levels were found to be significantly decreased in the presence of indomethacin, while no changes in LKB₄ levels were observed. DNA synthesis was inhibited by indomethacin, while protein synthesis was enhanced. Interleukin-6 levels were elevated in the absence of indomethacin. These results suggest that indomethacin may have confounding actions on tissue healing by decreasing DNA synthesis, yet stimulating protein synthesis.

The effects of piroxicam on the healing of ligament injuries were investigated after the severing of the medial collateral ligaments of rats.²⁸ Those treated with piroxicam for the first 6 days after injury demonstrated greater tetanic tension of the ligament at 14 days postinjury than those treated with a placebo. However, no significant differences in tetanic tension were noted at 21 days postinjury. Doubling or halving the dose of piroxicam given to the rats did not alter the findings. Administration of piroxicam after ligament injury did not yield detrimental effects on healing within 21 days of injury.²⁸

The results of these studies seem to demonstrate that NSAIDs are effective in reducing acute inflammation, but they may compromise the long-term healing of the injured tissue. Generalizing the results of animal studies to humans must be done cautiously. Animals' metabolism of NSAIDs may be different from that of humans, and it is difficult to estimate dose sizes comparable in animals and humans. While animal studies allow for excellent control of drug compliance, it is not possible to assess the effects of NSAIDs in conjunction with a structured rehabilitation program on the healing of acute soft tissue injuries.

Effects of NSAIDs on Delayed-Onset Muscle Soreness

The effects of NSAIDs on human muscle inflammation have been studied using the induction of delayed-onset muscle soreness (DOMS) after repetitive eccentric contractions as a model of muscle injury in humans. Bouts of eccentric exercise generate small amounts of muscle fiber damage and result in significant pain in the days after eccentric exercise.

Several authors have found no beneficial results when NSAIDs were administered before and after bouts of lower extremity eccentric exercise.²⁹⁻³¹ Flurbiprofen (150 mg/day) was not found to decrease subjective scores of pain or tissue damage markers on histologic examination of muscle when administered 6 hours before and for 72 hours after 30 minutes

of eccentric cycling.³¹ Administration of diclofenac (150 mg/day) 6 hours before and for 72 hours after 45 minutes of downhill running was not found to decrease soreness or tenderness and resulted in no alterations of blood chemistry when compared with a placebo.³⁰ In a follow-up study, subjects ingesting ibuprofen (2400 mg/day) before and after 45 minutes of downhill running had increased pain on palpation and elevated levels of serum creatine kinase and serum urea compared with those ingesting a placebo, suggesting that the ibuprofen may have contributed to further muscle damage.²⁹

Grossman et al³² found that subjects taking ibuprofen (2400 mg/day) before and after eccentric exercise of the elbow flexors had no differences in concentric or eccentric muscle strength, pain, or range of motion at 48 and 96 hours postexercise compared with a group taking a placebo.

In contrast, Hasson et al³³ found that those taking ibuprofen prophylactically (400 mg before exercise and 1200 mg/day after) had less pain and strength loss 24 hours after inducement of DOMS. Subjects who took ibuprofen either prophylactically or after the exercise (1200 mg/day) session had less pain and strength loss 48 hours after exercise than those taking a placebo.

The results show a consensus of studies demonstrating that NSAIDs do not adequately reduce the effects of DOMS after eccentric exercise. While DOMS models induce pain and some degree of myofibular disruption, prostaglandins do not appear to play as integral a role as they do in the inflammatory process accompanying actual muscle strains.³¹

Clinical Trials of NSAIDs in Sports Medicine

Clinical studies of the efficacy of NSAIDs on acute soft tissue injuries in the sports medicine setting have been highly criticized in previous literature reviews.^{22,34-36} Many studies have lacked quality research design methods such as not being conducted in a double-blind manner or not using a placebo control. Often two or more NSAIDs have been compared for efficacy, but no placebo was included in the study, so there was no way to verify that any of the NSAIDs yielded beneficial effects. In addition, the interval between injury and initial administration of the drug has often been poorly controlled. To truly identify the effects NSAIDs have on acute injuries, drug therapy should begin within 24 hours of injury.³⁴

Clyman²² has criticized previous studies for employing poorly defined subjective measurements rather than objective variables as indicators of healing. Other common problems with clinical trials have included several different types of injuries (eg, sprains, strains, contusions, tendinitis) in the same trial and poor control over the severity of injuries included in trials. Researchers have also tended to track injured subjects only for a short period of time, such as a few weeks, after injury and to not gather data regarding reinjury rates or long-term functional capacity and performance. The adverse effects of NSAIDs have also not been regularly examined. Furthermore, many researchers have failed to control for adjunct treatments including rehabilitation, immobilization, or weightbearing status.³⁴ Given these criticisms, readers must interpret the data from these studies cautiously.

A review of the ten placebo-controlled, scientifically sound trials investigating the effects of NSAIDs on acute soft tissue injuries since 1980 revealed that six found beneficial effects, three did not yield beneficial results, and one had conflicting results. Most benefits were seen in the first few weeks after injury, and no long-term benefits were seen. These findings may be attributable to the generally quick healing of strains and sprains regardless of different types of therapy.

Santilli et al³⁷ investigated the effects of piroxicam (20 mg/day), OTC ibuprofen (900 mg/day), and a placebo on soft tissue injuries in 30 professional athletes. Patients in all three groups improved significantly throughout the trial, although the piroxicam group demonstrated less pain and functional disability than the OTC ibuprofen and placebo groups.

McLatchie et al³⁸ examined 133 athletes suffering mild or moderate ankle sprains who were treated with either 600 mg ibuprofen four times daily, 1200 mg ibuprofen twice daily, or a placebo for 7 days. Those treated with either dosing schedule of ibuprofen had greater active range of motion 3 days postinjury, but no differences in motion were noted at 7 days. The ibuprofen groups did exhibit less joint tenderness and more functional capacity than the placebo group at 7 days.

Hutson³⁹ investigated the effects of two different daily doses of ibuprofen (1800 mg/day and 2400 mg/day) and a placebo on the recovery of 46 individuals who suffered ligamentous knee injuries. While significant improvements were seen in the level of joint effusion and pain in all three groups on days 7 and 14, those treated with ibuprofen returned to weightbearing sooner and had greater range of motion on days 7 and 14. The ibuprofen groups had a greater functional capacity than the placebo group at day 7 but not at day 14.

Lereim and Gabor⁴⁰ examined the effects of piroxicam (40 mg/day for 2 days, then 20 mg/day for 5 days) versus a placebo in 74 individuals suffering from a variety of lower extremity soft tissue injuries. At 3 days postinjury, the piroxicam group had significantly less pain at rest, with movement, and with weightbearing and less tenderness and functional limitation, as well as greater muscle strength, than the placebo group. However, at 7 days the only differences between groups were seen in strength and tenderness. On average, the piroxicam groups had complete relief from symptoms 2.7 days sooner than the placebo group.

Bahamonde and Saavedra⁴¹ studied the effects of diclofenac (150 mg/day), piroxicam (20 mg/day), and a placebo for 7 days on 93 subjects who sustained ankle sprains. After 2 days of treatment, diclofenac reduced pain at rest and while weightbearing to a greater degree than piroxicam or a placebo, but no differences were seen in edema. There were no differences in any of the dependent variables among the three groups after the medications were discontinued.

Giani et al⁴² utilized telethermography in addition to clinical examination to investigate the effects of a 7-day administration of diclofenac sodium (150 mg/day), suprofen (600 mg/day, an NSAID not available in the US), and a placebo on the outcome of 45 patients suffering acute musculoskeletal injuries. Diclofenac sodium was found to be superior to suprofen and placebo with regard to the physician's clinical evaluations, the

patients' subjective evaluations, and the telethermographic evaluation.

Jenner⁴³ performed a meta-analysis on the effects of nabumetone (2 g/day) with a placebo and with aspirin (2700 mg/day), ibuprofen (1600 mg/day), and naproxen (1000 mg/day) on 986 patients suffering from soft tissue and skin injuries. Drug therapy lasted for 7 days, and no significant differences were found between the placebo and nabumetone in regard to patient recovery. Nabumetone was found superior to aspirin in limiting pain and swelling, but inferior to naproxen in regard to pain. Nabumetone also yielded fewer gastrointestinal side effects than aspirin.

Dupont et al⁴⁴ compared the effects of ibuprofen (2400 mg/day) and a placebo on 61 athletes suffering acutely sprained ankles over the course of 8 days. An aggressive functional rehabilitation program was performed by all subjects. Subjects were evaluated for pain, tenderness, edema, and functional capacity at baseline and 4, 8, and 28 days after injury. No significant differences were found between groups, and the authors emphasized that the successful outcomes of the subjects may be linked to the aggressive rehabilitation program.

Fredberg et al⁴⁵ examined the effects of ibuprofen (2400 mg/day) and a placebo on 68 individuals who suffered acute ankle sprains. Subjects had their ankles immobilized in casts for 4 days after the initial examination and were then evaluated for changes in pain and ankle circumference on the fourth day of treatment. No significant differences were found between the ibuprofen and placebo groups for pain or joint circumference.

Slatyer et al⁴⁶ examined the effects of piroxicam (40 mg/day for 2 days, then 20 mg/day for 5 days) and a placebo on recovery from ankle sprain in 364 Australian military recruits. Subjects in both groups underwent a standard course of physical therapy and were evaluated at 3, 7, and 14 days and 1, 3, and 6 months after injury. The piroxicam group experienced less pain, was able to return to military training sooner, and had increased exercise endurance upon return to training over the placebo group. However, the piroxicam group also demonstrated a higher prevalence of positive anterior drawer signs and reduced ankle ranges of motion than the placebo group. These data suggest that, while piroxicam may help an injured individual return to activity sooner, adequate healing of injured tissues may not take place if an NSAID is administered in the days after acute injury. The authors reported a 25% recurrence rate within 6 months of initial injury, but they failed to identify any differences in recurrence between treatment groups.

These studies yielded conflicting results pertaining to the role of NSAIDs in the treatment of acute soft tissue injuries. These inconsistencies may be due to a number of factors, including the differences in drug choice and dosage and severity of injuries investigated. Given the disparity in these findings, it is difficult to either unequivocally advocate or condemn the use of NSAIDs in the treatment of acute soft tissue injuries. Those prescribing NSAIDs must be aware of the potential benefits and risks of these drugs as they relate to soft tissue healing.

The retarded healing of injured soft tissues after the administration of NSAIDs may be due to limiting development of the secondary zone of injury. If neutrophil and phagocyte migration are limited after injury, fibroblast and granulocyte activity may also be diminished in the days after injury. This may result in impaired scar tissue formation, thus leading to a subsequent decreased tensile strength of the mature scar tissue.

It is difficult to separate the anti-inflammatory and analgesic effects of NSAIDs in the treatment of acute injuries.⁸ Analgesia may allow increased range of motion earlier in the rehabilitation process and thus hasten the recovery process, regardless of the anti-inflammatory effects. Further research is needed to examine the effects of analgesics without anti-inflammatory effects, such as acetaminophen, in the treatment of acute athletic injuries.

Previous authors³⁴⁻³⁶ have expressed a need for better-controlled clinical studies to explore the efficacy of NSAIDs in the treatment of acute injuries. Future studies must use randomized, double-blind, placebo-controlled designs and also must limit the interval from injury to onset of drug therapy to less than 24 hours. In addition, rehabilitation and other adjunct therapies must also be controlled for and treated as independent variables. Including a control group consisting of injured subjects who receive neither NSAIDs nor a placebo will help to eliminate any placebo effects from the study. Dependent variables must include objective measurements of functional status and rates of reinjury in addition to the subjective assessments of pain and tenderness.

Adverse Systemic Effects of NSAIDs

As mentioned previously, aspirin was the original NSAID, but it was found to cause numerous adverse systemic effects in addition to its target analgesic, antipyretic, and anti-inflammatory effects. The other members of the NSAID class, while producing fewer adverse effects than aspirin, are also not free of side effects.

The most common side effects associated with NSAIDs are gastrointestinal ailments such as dyspepsia, nausea, gastrointestinal bleeding, and ulcers.^{12,34,47} These effects stem primarily from the inhibition of prostaglandins in the gastric mucosa. Prostaglandins normally decrease gastric acid secretion and increase bicarbonate and mucus secretion; however, in the presence of prostaglandin-inhibiting drugs, these protective mechanisms cannot occur.⁷ Gastrointestinal symptoms are most often related to chronic NSAID use but may also be seen with short-term use.⁷

Gastrointestinal effects may be reduced by the concurrent prescription of a cytoprotective medication, such as an H₂ blocker or misoprostol.⁹ Etodolac, a member of the pyranocarboxylic acid class, does not inhibit prostaglandin synthesis in the gastric mucosa; therefore, ingestion of etodolac is associated with fewer serious gastrointestinal effects than other NSAIDs.⁷ In addition, ingestion of NSAIDs with food appears to decrease gastrointestinal distress.⁴⁸

Some NSAIDs, especially aspirin and the salicylates, are known to impair normal coagulation by inhibiting platelet aggregation. This effect is potentially harmful during periods

of acute inflammation because it may lead to a greater area of initial hematoma after injury. The adverse effects on clotting mechanisms associated with NSAIDs are of particular importance in individuals who have a coagulopathy or a closed head injury.⁴⁸ Aspirin permanently inhibits cyclooxygenase for the length of an erythrocyte's life and can thus impair clotting for up to a week after injury.⁴⁹ Non-traumatic compartment syndrome has been reported following ingestion of aspirin 2 days after a muscle strain injury.⁵⁰ NSAIDs should be avoided when an individual is taking anticoagulant medications, such as coumadin and warfarin.^{5,10} NSAIDs are sometimes prescribed specifically for their anticoagulant effects in the treatment of conditions such as deep vein thrombosis.¹²

A less common side effect involves renal dysfunction after the ingestion of NSAIDs.²³ This effect is most often seen in the elderly and those with previous kidney damage and thus is less likely to occur in the athletic population.¹² Prostaglandins are involved in the regulation of normal renal homeostasis; therefore, normal renal function can be inhibited by NSAIDs. Calabrese and Rooney⁴⁷ caution against the use of NSAIDs by individuals who are dehydrated because of the possibility of causing renal damage.

Aspirin sensitivity is an allergic reaction resulting in urticaria, angioedema, and asthma. Those with aspirin sensitivity should avoid all NSAIDs.^{9,47}

Other side effects occasionally associated with NSAID use include hepatic damage and central nervous system dysfunction. Liver damage typically occurs only in individuals who have suffered previous liver damage.¹² The most common central nervous system effects include headache, tinnitus, and drowsiness.¹²

Limitation of side effects is best achieved via careful monitoring by the prescribing physician and other health care providers of patients prescribed NSAIDs. It should also be noted that many of the adverse effects are associated with chronic NSAID use. Prescription and OTC NSAID use by athletes must be closely monitored by all health care providers.

CONCLUSIONS

NSAIDs are commonly used in the treatment of acute soft tissue injuries in athletes, yet their efficacy is not substantiated in the scientific literature. While NSAIDs are often prescribed for their anti-inflammatory, analgesic, and antipyretic effects after acute injury, there is little evidence to support the claim that NSAIDs hasten the return of injured athletes to competition. In addition, separating the anti-inflammatory effects from the analgesic effects is not easy. Recent evidence from studies using animal models suggests that the short-term benefits of NSAIDs may be outweighed by long-term compromise of the structure and function of the injured tissue.

Because of the numerous adverse effects associated with NSAIDs, athletic trainers must be aware of the potential benefits and liabilities of NSAID use by injured athletes. Further research must address the effectiveness of NSAIDs in clinical trials involving injured athletes. Current research

demonstrates that NSAIDs may be beneficial in hastening the return to competition by injured athletes but also that NSAIDs should be only one part of the total treatment plan. NSAIDs do not take the place of therapeutic modalities and exercise and must be considered as an adjunct to rehabilitation rather than the most direct route to recovery.

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