Highlights Newsletter

from the open-session symposium held during the 54th Annual Meeting & Clinical Symposia of the National Athletic Trainers' Association

Analgesia in Sports Medicine: Integral Issues for the Sports-Related Injury

Official Sponsor

National Athletic Trainers' Association

McNeil Consumer & Specialty Pharmaceuticals

This program is supported by an unrestricted educational grant from McNeil Consumer and Specialty Pharmaceuticals.

Introduction and Overview

Athletes frequently use over-the-counter (OTC) analgesics and anti-inflammatory medications for sports-related injuries. The benefits and risks of these drugs for the treatment of common sports injuries need to be considered explicitly. Although these drugs are easily obtained, they are medications with the ability to affect human physiology. The decision to use pain medication should be one that is well thought out—even when the decision involves over-the-counter medications.

This newsletter is written to inform the practicing athletic trainer about current clinical viewpoints on prescription nonsteroidal anti-inflammatory drugs (NSAIDs) and their OTC alternatives. Cyclooxygenase (COX)-2–specific NSAIDs, which are prescription medications, are also discussed because they involve similar treatment issues. The topics covered include the role of inflammation in sports injuries of soft tissue and bone; how anti-inflammatory medications impact healing of these injuries; and the safety profiles of these medications.

The articles presented herein are based on presentations given by the authors at a symposium held at the Annual Meeting of the National Athletic Trainers' Association in St. Louis, Missouri on June 26, 2003. Unrestricted funding for the symposium was provided by McNeil Consumer & Specialty Pharmaceuticals.

Joseph Bernstein, MD
Assistant Professor of Orthopedic Surgery
Department of Orthopedic Surgery
University of Pennsylvania School of Medicine

Steven Stovitz, MD, CAQ Sports Medicine
Assistant Professor
Chairman of Sports Medicine Curriculum for the Family Practice Residency Programs
Department of Family Practice and Community Health
University of Minnesota

Edwin Kuffner, MD
Attending Toxicologist
Rocky Mountain Poison and Drug Center
Toxicology Consultant
University of Colorado
Denver Health Medical Center
Porter and Littleton Hospitals

The Role of Inflammation in the Healing of Soft Tissue Sports Injuries

Steven Stovitz, MD, CAQ, Sports Medicine

Among the most common sports-related soft tissue injuries are stretch-induced muscle injuries (strains), muscle contusions, and delayed-onset muscle soreness, as well as injuries to tendons and ligaments. Inflammation is an early (and necessary) part of the wound healing process in each type of injury. Over-the-counter (OTC) pharmaceuticals that reduce pain and inflammation have a role in the rehabilitation and healing of these injuries, but may be evaluated in light of their specific therapeutic properties. The need to reduce, but not eliminate, pain must be weighed against interfering with the natural and necessary process of inflammation.

The Wound Healing Process

Wound healing occurs in 3 phases, each of which is a necessary step in the process. The inflammatory phase begins within minutes to hours after injury and is characterized by an influx of inflammatory cells to the site of injury. These cells include neutrophils, which clear away necrotic muscle fibers and cellular debris,[1] and may be involved in the production of free radicals and intercellular signaling proteins known as cytokines.[2] In addition, macrophages are recruited to the injury site. ED^{1+} macrophages invade the damaged muscle fiber and destroy cellular debris and damaged myofibrillar material.[2] In the proliferative phase that follows, ED^{1+} macrophages continue to remove debris. ED^{2+} macrophages arrive and produce growth factors, which recruit fibroblasts and cytokines that may regulate the proliferation or differentiation of myoblasts, the cells that create new muscle tissue.[2] Finally, in the maturation phase, fibroblasts lay down collagen and tissue remodeling takes place.

The time required for all 3 phases of the wound healing process is variable: it can take from days to months depending on the extent of the injury. Because the inflammatory phase is essential for the subsequent phases to take place, it is critical to the healing process. This is an important consideration when selecting and recommending drug therapies.[2,3]

> *"Inflammation and repair are parts of a single process, the response to injury."*[4]
>
> *"Inflammation can occur without healing, but healing cannot occur without inflammation."*[5]

Pharmaceuticals

Among the OTC pharmaceuticals available for treating musculoskeletal injuries are aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. While NSAIDs have antipyretic (fever-reducing) and analgesic action, they have been emphasized historically in sports medicine for their anti-inflammatory properties. However, this emphasis may be misplaced. Acetaminophen also has antipyretic and analgesic actions, but minimal anti-inflammatory effects, if any.

The mechanisms of action and adult dosing recommendations for the drugs, along with a discussion of their adverse effect profiles, can be found in the accompanying article by Dr. Kuffner.

Tendon Injuries

In the classic model, tendon injury was thought to result in swelling and pain due to inflammation, thus putting the "-itis" in "tendinitis." Therapy was focused on reducing the inflammation with rest, ice, and anti-inflammatory medication in order to decrease the swelling and pain. However, this model is no longer seen as clinically valid. In the case of chronic tendon injuries, the reason is simple—they are not inflammatory. A review of 2326 articles on the etiology, diagnosis, and treatment of tendinitis found no studies clearly supporting an inflammatory etiology.[6]

Similarly, chronic tendon injuries such as tennis elbow are often called tendinitis. Biopsy studies show that these injuries are due to microtrauma of

the tendon, with pain arising from irritation of nearby structures (the paratenon and bursa); inflammation is not involved.[7,8] For tendon degeneration without signs of inflammatory response, the more appropriate term is "tendinosis." The generic term for all pathologies that arise in and around tendons is "tendinopathy." The differences between these terms are not merely semantic—there are clinical implications. If the pathology in most cases is tendinosis, then treatment needs to combat collagen breakdown rather than inflammation.[9]

"It appears that tendinosis is the major, perhaps the only, clinically relevant chronic tendon lesion."

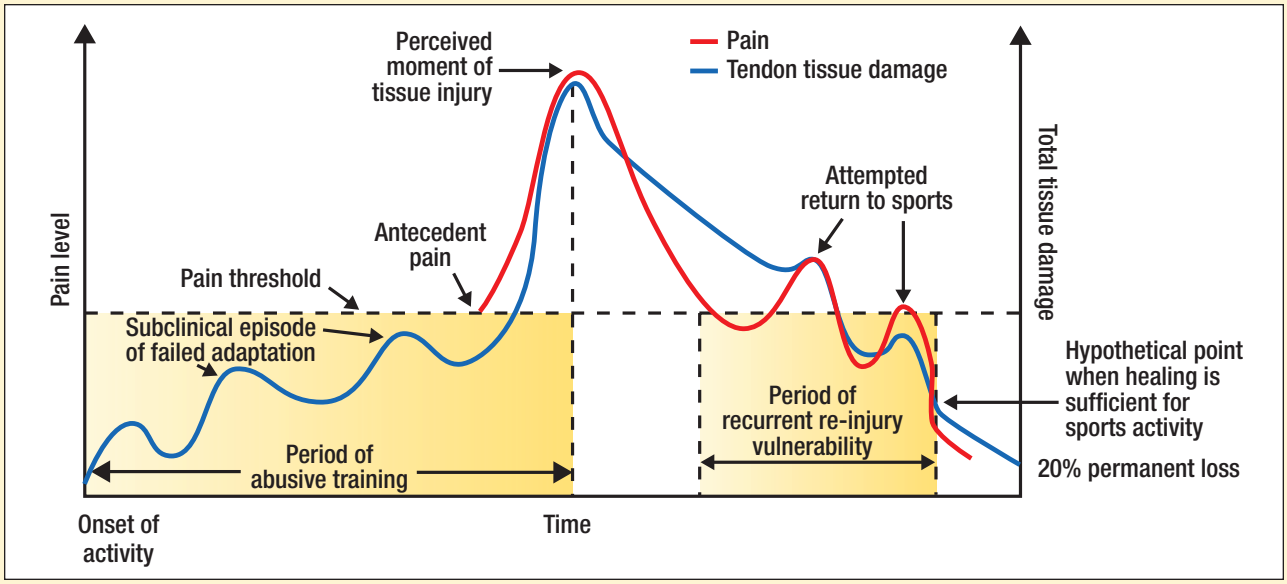
Less is known about acute tendon injuries, because they are not typically biopsied. One theory is that tissue damage in overuse tendinopathy may actually precede acute injury and overt symptoms,[10] a sequence of events illustrated in Figure 1. In sports medicine, a typical scenario is a period of excessive training that precedes the development of symptoms. A tennis player might complain of elbow pain after lifting a bag of groceries, but there is no way to determine whether this is really an acute injury or whether there was preexisting tendon damage.

Given what we know about tendon injuries, how should we treat them? NSAIDs have effects on both inflammation and pain. In theory, the anti-inflammatory effects would appear to have little therapeutic benefit in tendinosis.[7] A literature review indicates that actual improvement in the healing process has not been studied.[6] The analgesic effects may be beneficial because reducing pain may allow for appropriate physical therapy and rehabilitation. A review of NSAIDs and chronic tendon injuries found only 9 prospective, placebo-controlled studies. Five of these 9 studies showed improved pain scores in the NSAID group, and the maximum follow-up was only 1 to 4 weeks.[6] According to Almekinders and Temple, "it remains to be determined whether NSAIDs actually change the natural history or whether they merely have some analgesic action in these injuries."[6]

There are also clinical implications for physiotherapy. For example, rest decreases inflammation, but increases the risk of tendon degeneration. Eccentric

FIGURE 1

Pain and Tissue Damage in Overuse Tendinopathy May Precede Acute Injury



Schematic illustration of pain and tissue damage in overuse tendinopathy. Tendon pathology may begin well before symptoms arise. Therefore, recovery may take months, even in patients who present with recent onset of symptoms.

Reprinted with permission from Leadbetter W, et al, eds. *Sports-Induced Inflammation*. Park Ridge, Ill: American Academy of Orthopedic Surgery; 1990.

muscle training increases inflammation, but decreases the risk of degeneration. The benefits of eccentric strengthening have been shown in chronic Achilles tendinosis.[11,12] The current physical therapy recommendations are relative rest and eccentric strengthening of muscle. Analgesics may help with the rehabilitation process, but, paradoxically, they may allow the athlete to continue abusing the tendon.

Ligament Injuries

The clinical literature on ligament injuries focuses on joint function, not ligament healing. Doctors rarely visualize the ligament itself, and thus rely on functional assessment and patient reports to evaluate progress. Nevertheless, 2 principles have been repeatedly validated in studies. The first is that early mobilization of the joint results in faster healing. The second is that controlled rehabilitation (avoiding excessive stress) helps speed recovery.

A literature review examined 8 placebo-controlled studies of NSAIDs in injuries to a single type of ligament.[13] In the 6 studies of ankle ligament injuries, 2 found NSAIDs to be better than placebo in reducing pain and 4 found no difference. In 2 studies of knee injuries, NSAIDs performed better than placebo. The review authors conclude that the literature does not provide uniform support to the assumption that NSAIDs provide quicker or better recovery.[13]

According to another review of ankle injuries, NSAIDs used soon after injury and for short periods of time were "of value in achieving early recovery," but did not alter the overall clinical outcome.[14] Ligament-injured joints heal best with early, controlled mobilization.[15] If NSAIDs or acetaminophen promote mobilization, then their use is likely to be beneficial.

Muscle Injuries

Among the most frequent types of sports-related muscle injuries are strains, contusions, and delayed onset muscle soreness (DOMS).[3] Strain injuries are the result of excessive tension on the muscle, that results in a tear, followed by inflammation, clearing of debris, and finally regeneration of the muscle. Do NSAIDs help or hinder the healing process? Animal studies show that NSAIDs may result in delayed healing.[3] A rare human study on the topic compared NSAIDs to placebo in treating acute hamstring injuries and found no benefit to NSAIDs in terms of pain assessment, swelling measurement, or isokinetic muscle performance.[16]

Contusions are the result of a direct blow to the muscle, resulting in a hematoma with inflammation in the muscle belly, and perhaps periosteal contusion. There have been no studies in humans on the relation of NSAID use to the healing of muscle contusion injuries.[3,17]

In general, DOMS begins 24 to 48 hours after intense eccentric muscle use. Consensus opinion is that inflammation is not an essential feature of DOMS; therefore, NSAID use is not likely to be of great benefit. Human studies bear this out—as a whole, they are equivocal as to whether NSAIDs help or hinder the healing of DOMS.[3]

Conclusions

Inflammation is a result of injury and a necessary step in the healing process. Soft tissue injuries tend to heal with controlled mobilization and rehabilitation. As to the role of pharmaceuticals and the healing of athletic injuries, research is very limited. Because chronic tendon injuries do not have an inflammatory component, the anti-inflammatory properties of NSAIDs are of little benefit in treatment. Pain relief likely has a therapeutic benefit when it encourages mobilization and rehabilitation.

Recommendations

In dealing with soft tissue sports injuries, accurate diagnosis is paramount. Athletic trainers need to understand the relevant pathophysiology, including the biomechanics of the injury, the healing process, and its time course. Along with soft tissue injuries comes pain, which is closely tied to issues of performance for athletes. It is important to separate the problem from the pain, then treat them both. Knowledge of treatment side effects is valuable in selecting and monitoring a course of treatment with OTC analgesics.

Bone Injury and Repair

Joseph Bernstein, MD, MS, Orthopedic Surgeon

In this article, stress fractures are used to illustrate the process of bone injury and repair and to consider the therapeutic use of OTC analgesics in managing pain and inflammation during the healing process. Stress fractures are used as a paradigm for athletic injury. By considering the biology of bone and its repair, 2 key themes, applicable to many sports injuries, emerge. The first is that the goal of treatment is to limit, but not eliminate pain. Pain is a signal that helps modulate activity—a signal that is ignored only at great risk (stress fractures can become "real" fractures). The second, complementary theme is that treatment should at most limit, but not eliminate inflammation. Inflammation is there for a reason. In bone injury, inflammation initiates repair—inhibit inflammation and you likewise inhibit repair. Thus, the wise patient, counseled by a wise trainer, will use an OTC analgesic that allows for pain relief and appropriate activity, but, following the first rule of medicine, does no harm.

Stress Fractures as a Paradigm

There are several reasons why stress fractures are an excellent paradigm for discussing sports injury and the process of repair. The obvious reasons are that stress fractures are common, and, perhaps more so than other injuries, uniquely associated with sports activity. Beyond that, there are a few other reasons. For one, radiographic imaging techniques allow us to chart the progress of a stress fracture and its repair. We can literally see how well (or not well) the treatment methods work—and, in bone, what you see is what you get. This stands in contrast to ligament. A stretched ligament does not necessarily have any functional consequences. A patient could compensate for ligament laxity with muscular action. There is no such substitute for the skeletal function of bone. With a stress fracture, we know how well the patient is doing. Stress fractures are also an apt topic for study because the biology of their healing, and the healing of fractures in general, is well described.

Sophisticated imaging techniques allow us to chart the progress of a stress fracture and its repair. Standard radiography is not useful in the early detection of these injuries, but magnetic resonance imaging lets us see the bone abnormalities weeks before they appear on X-rays.[18] Bone scans (scintigraphy) have a high sensitivity for detecting stress fractures.[18] In this technique, a tracer material is taken up by areas of the bone where metabolic activity is high, such as the epiphysis or the site of a stress fracture. In the latter case, the increased metabolic activity is due to the action of osteoclasts and osteoblasts as they repair the injured bone.

Stress fractures heal the same way as all other fractures. The process, called endochondral ossification, involves the formation of bone via a cartilage intermediate,[19,20] the normal sequence of events in skeletal growth.[20] Stress fractures comprise about 1% to 16% of all injuries sustained by athletes[21] and can account for up to 10% of patients at a typical sports medicine practice.[18]

In sum, stress fractures are a common athletic injury, involving a system whose biology is fairly well understood; whose healing can be visually monitored; and whose function, or lack of function, can be deduced on clinical exam with great specificity.

The Biology of Bone

Bone is alive. It provides structure to the body, serves as a mineral reserve bank, and houses the machinery of blood cell formation. Specialized cells maintain the skeleton: osteoclasts resorb bone and osteoblasts create new bone. Most bone forms on a cartilage model. This process also occurs during fracture healing to convert the cartilaginous scar into new bone. In this respect, skeletal repair mimics the process by which the skeleton is formed in the first place. The implication for pain management is that medications that adversely affect skeletal development may also inhibit bone formation during fracture healing.

Bone constantly repairs itself in a process called bone remodeling. Remodeling in the adult frees minerals from the skeleton and removes areas of damaged bone.[18] Both chemical signals (such as low calcium or estrogen) and mechanical signals

(load) modulate the remodeling process. In women during menopause, when estrogen levels decline, osteoclast activity may exceed that of osteoblasts, leading to decreased skeletal mass.

Mechanical load stimulates remodeling. Bone is deposited in areas where load bearing is high and is removed from areas where there is inadequate stress. Too much load causes skeletal damage; not enough load (as occurs in weightlessness) leads to abnormal bone tissue as well.

Stress Fractures

Stress fractures of bone do not result from a single traumatic event. They are the result of the repetitive strain that bone undergoes when placed through multiple loading cycles. Over time, cyclical loading can lead to local microscopic changes in the normal trabecular architecture of bone. Stress fractures are thought to account for between 1% and 10% of all sports injuries and 5% to 15% of all running injuries.[22] There is a predilection for females, nearly 2 to 1, and Caucasians, almost 10 to 1.[21] In osteoporotic or other forms of abnormally weakened bone, fatigue fractures are known as "insufficiency" fractures. Patients with stress fractures typically describe history of a change in activity prior to the onset of pain. Often, patients with stress fractures will complain of a gradual onset of pain with activity. Without treatment, the pain associated with these fractures occurs earlier in the activity cycle and takes longer to abate after cessation of activity. The pain also becomes more localized over time. Physical examination reveals localized tenderness and sometimes swelling, but limited redness and warmth in the affected area. There is often a normal range of motion and strength of the affected bone. More than 95% of these injuries occur in weight bearing structures such as the tibia, the metatarsals, the spine, and the pelvis—the structures most susceptible to repetitive loading.[23] However, a variety of sites may be affected, including many non-weight bearing bones.

Plain film radiography may be sufficient for diagnosis. Plain films may reveal radiolucency in the affected bone, callus formation, or sclerotic changes. However, plain film radiography is diagnostic in only about a third of all cases and has an overall sensitivity of, at best, 50%.[24] Bone scintigraphy can visualize a stress fracture as a focal increase on delayed images of a triple phase scan and can be positive as early as 24 hours after injury. Magnetic resonance imaging (MRI) can also be used to evaluate suspected stress fractures.[24] MRI offers excellent evaluation of soft tissues and will reveal edema within the bone at sites of stress fractures.

Overt fractures are more obvious and easier to diagnose than stress fractures. The changes are macroscopic and apparent on physical and radiographic examination. In terms of the pathophysiologic response to injury, however, overt fractures share some characteristics with stress fractures. One key similarity is that regardless of type, fractured bone has the potential to completely regenerate.

Normal, healthy bone undergoes constant remodeling resulting from the activity of osteoblasts and osteoclasts. In a sense, a natural "inflammatory" process is always present in bone—recruitment of cells, resorption, and repair are required for normal skeletal maintenance. Fracture healing employs these mechanisms, though the inflammatory response is more pronounced in reaction to an overt fracture, probably because the bleeding associated with overt fracture stimulates a more intense response. Osteoclasts remove damaged or necrotic bone; osteoblasts replace the injured tissue with new, healthy bone.[21]

Pain Medication for Stress Fracture

The ideal analgesic for fracture will control pain without interfering with normal healing and remodeling. Pain control is important for healing fractures. Without analgesia, the patient may be unwilling to bear weight—even at a point in the healing process where weight bearing is not only harmless, but is required for tissue repair. The need for some weight bearing is a consequence of Wolff's Law of Transformation: bone grows in response to mechanical stimulation. At the same time, too much weight bearing is harmful. Thus, there is a need to maintain some sense of pain. This provides a feedback signal to protect the injured patient from too much activity, which can be detrimental to fracture healing.

While control of inflammation can contribute to pain relief, it is important to note that the activities of inflammatory mediators influence the repair process. Accumulating evidence reveals that

prostaglandins affect both osteoclastic and osteoblastic activity and may be necessary for optimal healing. Specifically, data suggest that NSAIDs can inhibit bone healing and even the new cyclooxygenase (COX)-2 inhibitors, generally considered safer than nonspecific inhibitors, may not be appropriate for pain relief during a period of bone healing.[25] The selectivity of COX-2 inhibitors in this context makes intuitive sense. COX-2 inhibitors block production of inflammatory prostaglandin synthesis, the prostaglandins involved in bone healing. This is not a matter of "good" prostaglandin synthesis versus "bad" prostaglandin synthesis, but rather whether inhibition of inflammation at the site of bone healing is harmful. In a recent editorial, Dr. Thomas Einhorn suggests temporary avoidance of cyclooxygenase inhibitors during a period of bone healing.[25]

In differentiating the potential roles of the 2 major cyclooxygenases, some studies reveal that COX-1 is more important than COX-2 for bone healing. COX-2 inhibitors have been shown to have a limited effect on the fusion rate after spine surgery in a rat model, and NSAIDs have been shown to result in an increased rate of pseudoarthroses in the spine.[26] However, a recent study in COX-2 deficient mice has shown a delay in callus formation and union of fractures, while the COX-1 deficient mice did not have difficulty in bone repair.[19] In that same study, the COX-2 deficient mice failed to exhibit the ability to perform intramembranous bone formation via direct bone deposition.[19]

These results were supported by others in a rat model, where there was significantly greater inhibition of callus formation and fracture healing by COX-2 specific inhibitors as compared to nonspecific NSAIDs and controls.[20] To add to the confusion, another study using the rabbit bone ingrowth model indicated that both COX-1 and COX-2 may be important for proper bone healing.[27]

In light of the data suggesting that NSAID use or COX-2 inhibitor use might inhibit bone healing, it is worth noting that only 1 retrospective case-control study reveals a higher rate of nonunion. Giannoudis and colleagues[32] compared patients who developed nonunion of the femoral shaft with 67 case-control patients whose femoral fracture had united.[28] They found a highly significant statistical association (P=.000001) between the use of NSAIDs following the injury and femoral nonunion.[28] It is important to note, however, that there are some fractures for which NSAID (or COX-2 inhibitor) use is clearly beneficial; namely those fractures associated with a high risk of heterotrophic ossification.

More studies are necessary to resolve differences between study results reported so far. But the implication is clear: prostaglandin inhibition may have a significant impact on healing bone. Patients at an already heightened risk for nonunion (endocrinopathic, osteoporotic, smokers) and those undergoing significant active bone healing (post fracture repair, etc) should be particularly cautious. Trainers must reinforce this message when discussing pain medication with athletes.

Over-the-Counter Analgesics: What Athletic Trainers Need to Know

Edwin Kuffner, MD, Toxicologist and Emergency Physician

The purpose of this article is to discuss the common OTC analgesics, their mechanisms of action, and their safety profiles. The recommended adult doses will be discussed, and the adverse effects of these medications will be reviewed. Special attention will be given to overdoses, the situations in which they occur, and how athletic trainers can help prevent them.

OTC Analgesics

Some common OTC analgesics are listed in Table 1. Acetaminophen is the active ingredient in the Tylenol® brand (in all its variants). However, many other OTC medications contain acetaminophen, a point discussed further below. Aspirin is less commonly used among athletes and by the younger generations generally. NSAIDs include ibuprofen, the active ingredient in Advil® and Motrin®, naproxen sodium (Aleve®), and ketoprofen (Orudis®).

Mechanisms of Action

Acetaminophen's mechanism of action is unknown. Unlike aspirin and NSAIDs, it does not inhibit prostaglandin synthesis. There is speculation that it increases the pain threshold by inhibiting COX-3 in the brain and spinal cord, but this requires further study. Aspirin and NSAIDs inhibit the activity of the cyclooxygenases known as COX-1 and COX-2. These enzymes are responsible for the synthesis of prostaglandins, which in turn sensitize pain receptors. By decreasing prostaglandin synthesis, aspirin and NSAIDs reduce the sensitivity of pain receptors to the initiation of pain at sites of injury.

Prostaglandins are mediators of the inflammatory response that causes pain and swelling. They also play an indirect role in the healing of soft tissue injuries by regulating antibody production of lymphocytes and controlling macrophage collagenase production.[13] By blocking these actions, COX-1 and COX-2 inhibitors may also interfere with healing. Acetaminophen, which does not block prostaglandin production, does not impair the healing process.

Drugs which selectively inhibit COX-2 enzymes, including rofecoxib (Vioxx®) and celecoxib (Celebrex®), were not included in the list of OTC analgesics because they are prescription medications.

TABLE 1

Common OTC Analgesics

- Acetaminophen (Tylenol®)
- Aspirin
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
  - Ibuprofen (Advil®, Motrin®)
  - Naproxen sodium (Aleve®, Naprosyn®)
  - Ketoprofen (Orudis KT®, Actron®)

TABLE 2

Recommended Adult Doses of OTC Analgesics

Analgesic	Recommended dose (mg)	Frequency	Maximal daily dose (mg)
acetaminophen	650 to 1,000	every 4 to 6 hrs	4,000
aspirin	650 to 1,000	every 4 to 6 hrs	4,000
ibuprofen	200 to 400	every 4 to 6 hrs	1,200
naproxen sodium	220	every 6 to 8 hrs	660
ketoprofen	12.5 to 25	every 6 to 8 hrs	75

Recommended Adult Dosages

For acetaminophen, the maximum daily adult dose is 4,000 mg, the equivalent of 2 Extra Strength Tylenol (500 mg) 4 times a day.[29] The 4,000 mg/d limit should not be exceeded. The maximum OTC daily dose of ibuprofen is 1,200 mg, taken in doses of 200 to 400 mg every 4 to 6 hours. Adult dosages for the other OTC analgesics are listed in Table 2.

Safety and Tolerability

Aspirin, acetaminophen, and NSAIDs have considerable differences in their safety profiles. When

reviewing adverse effect profiles, it is important to distinguish between effects seen at therapeutic doses and those seen with overdose.

Overdose can be intentional or unintentional. While intentional overdose with OTC analgesics is not frequently seen in athletes, it is one of the most common overdose situations seen in the emergency room. The more frequent scenario among athletes is unintentional overdose. An athlete may assume that OTC medications are safer than prescription medications and deliberately take more than the recommended dose. He or she may fail to follow the OTC package labeling in hopes of faster pain relief or increased effectiveness. Studies on OTC analgesic use have found that >40% of patients take more than the recommended number of doses in a day; 69% take more than the recommended dose at a single time; and 63% take the next dose sooner than recommended.[30]

In other situations, an athlete will overdose by unknowingly combining different formulations or different products that contain similar active ingredients. Many athletes and athletic trainers are unaware that many common cough and cold preparations and prescription medications also contain acetaminophen (Table 3). It is the athletic trainer's responsibility to know and advise athletes on the active ingredients in common pain medications.

Acetaminophen. When the nontoxic parent compound of acetaminophen is metabolized in the liver, it produces a toxic intermediate. At therapeutic doses, the body easily detoxifies this toxic intermediate. Consequently, when taken at therapeutic doses, acetaminophen is extremely safe, even with prolonged use for chronic athletic injuries.

Overdose is the primary medical risk of acetaminophen. Following an overdose, the liver is unable to detoxify the toxic metabolite, which then binds to and kills liver cells. Large overdoses (usually greater than twice the maximal recommended daily dose, and more commonly 4 to 5 times as much) can cause liver damage or liver failure. Fortunately, there is an antidote. If administered within 8 hours of an acute acetaminophen overdose, survival and complete recovery is virtually guaranteed. It is important to note that most life-threatening incidents with acetaminophen are due to intentional overdose.

NSAIDs. Unlike acetaminophen, NSAIDs are more dangerous at therapeutic doses and relatively safer in overdose. At therapeutic doses, NSAIDs present an elevated risk of gastrointestinal (GI) bleeding and ulcers due to decreased prostaglandin production. Chronic therapeutic doses of NSAIDs can result in kidney damage. In otherwise healthy patients such as athletes, however, once the medication is halted kidney function returns to normal. It has been estimated that in the United States there are 16,500 deaths annually among patients with rheumatoid arthritis or osteoarthritis, including some athletes, who use NSAIDs therapeutically.[31] To put this figure in perspective, it is similar to the number of annual AIDS-related deaths and is greater than the annual deaths due to multiple myeloma, asthma, Hodgkin's disease, or cervical cancer.[31] Following even a large overdose, the adverse effects of NSAIDs are rarely life threatening; indeed, NSAIDs are the safest OTC analgesics in overdose.

Aspirin. In prolonged use at therapeutic levels for chronic athletic injury, aspirin can cause ulcers, GI bleeding, and even kidney damage. Even the daily dose of baby aspirin typically taken by the elderly for cardioprotective purposes carries an increased risk of these adverse effects. Large overdoses of aspirin (at multiples of 2 to 5 times the recommended maximal dose) can cause metabolic derangements, coma, seizures, and hyperthermia.

Other Dosing and Safety Issues

Alcohol. Despite the ubiquitous "alcohol warning" on labels of OTC analgesics, the best evidence to date suggests that, at the maximal recommended dose, acetaminophen is safe for athletes who drink alcohol and even for alcoholics.[32,33] In contrast, the best evidence for aspirin and NSAIDs suggests that alcoholics and athletes who drink alcohol are at increased risk of upper GI bleeding, a risk that is independently elevated by alcohol consumption.[33,34]

Combining OTC Analgesics. A question frequently asked by athletic trainers is whether it is safe to take acetaminophen and ibuprofen together. Because they have different mechanisms of action, it is safe to combine them. When an athlete requires more analgesia and is already taking the maximum recommended dose of one of these drugs, it is acceptable to treat with the other drug as well.

With the exception just mentioned, it is best not to combine OTC medications. Different products often contain similar active ingredients (Table 3). For example, it is easy to exceed the maximum daily dose of acetaminophen by inadvertently taking an OTC cough and cold medication or a prescription medication that also contains this active ingredient.

Age and Body Size. Athletic trainers who work with teenagers often ask whether these athletes should take the same dose as adults. There are pediatric preparations for most of the OTC analgesics. When determining dose, the most conservative recommendation would be to calculate the pediatric dose (milligrams/kilogram) and compare this to the usual adult dose. If the pediatric dose calculated based

TABLE 3

Overdose Risk: Different Products With Similar Active Ingredients

Prescription Products Containing Acetaminophen

Acetaminophen and Codeine Phosphate Oral Solution and Tablets
Anexsia® Tablets
APAP, Acetaminophen Uniserts/Suppositories
Axocet® Capsules
Butalbital, Acetaminophen and Caffeine Tablets
Capital® and Codeine Oral Suspension
Darvocet-N® 100 Tablets
Endocet Tablets
Esgic® Capsules and Tablets, and Esgic-Plus™ Tablets
Floricet® Tablets
Hycomine® Compound
Hydrocet® Capsules
Hydrocodone Bitartrate and Acetaminophen Tablets, Capsules, Elixir
Lorcet® Tablets, Capsules, HD, Plus
Lortab® Tablets and Elixir
Midrin® Capsules
Norco® Tablets
Norel Plus® Capsules
Oxycodone and Acetaminophen Tablets and Capsules
Pentazocine HCl & Acetaminophen Tablets
Percocet® Tablets
Phenaphen® with Codeine Capsules
Phrenilin® Tablets, Forte Capsules
Propoxyphene HCl and Acetaminophen Tablets
Propoxyphene Napsylate and Acetaminophen Tablets
Roxict™ Tablets, Caplets, Oral Solution
Talacen® Caplets
Tylenol® with Codeine Tablets and Elixir
Tylox® Capsules
Ultracet™ Tablets
Vicodin®, Vicodin ES®, Vicodin HP® Tablets
Wygesic® Tablets
Zebutal® Capsules
Zydone® Tablets

Nonprescription Products Containing Acetaminophen

Actified®: Cold & Allergy, Sinus
Alka-Seltzer Plus®: All Products
Anacin®: Aspirin Free Formula
Benadryl®: Allergy Sinus Headache, Severe Allergy & Sinus Headache
Comtrex®: All Products
Contac®: Severe Cold and Flu Maximum Strength Caplets, Non-Drowsy Caplets, Day & Night Cold & Flu
Coricidin®: D Cold, Flu & Sinus Tablets; HBP Cold & Flu Tablets
Dimetapp®: Non-Drowsy Flu Syrup
Dristan®: Cold Multi-Symptom Formula
Drixoral®: Allergy Sinus, Cold & Flu
Excedrin®: All Products
Feverall®: Suppositories
Goddy's® Powders: All Products
Midol®: Maximum Strength Menstrual Formula, Maximum Strength PMS Formula
NyQuil®/DayQuil®: Cold/Flu Relief Liquid and LiquiCaps
Pamprin®: All Products
Percogesic®: All Products
Robitussin: Cold, Multi-Symptom Cold & Flu, Multi-Symptom Honey Flu Liquid, Nighttime Honey Flu Liquid
Singlet®: Tablets
Sinutab® Sinus: Sinus Allergy Medication Maximum Strength Formula
Sudafed®: Cold & Cough Liquid Caps, Cold & Sinus Liquid Caps, Severe Cold Caplets and Tablets, Sinus Caplets and Tablets
Travist®: Sinus Non-Drowsy Coated Caplets
TheraFlu®: All Regular and Maximum Strength Caplets and Hot Liquid
Triaminic®: Cold, Cough & Fever Liquid; Cough & Sore Throat Liquid, Cough & Sore Throat Softchews
Tylenol®: Allergy Sinus Formula, Severe Allergy; Arthritis Pain Extended Relief; Cold Formula, Cold & Flu; Extra Strength Pain Reliever; Flu Formula: Maximum Strength Sore Throat Adult Liquid; PM Pain Reliever/Sleep Aid; Regular Strength; Sinus; Women's Tylenol
Vanquish®: Caplets
Vicks®: Vicks 44M Cough, Cold & Flu Relief Liquid and Liquicaps

upon the patient's weight is less than the adult dose, this dose should be recommended. Obviously, if the pediatric dose calculated based upon the patient's weight exceeds the adult dose, the adult dose should be recommended. Most teenagers of average weight can safely take adult doses.

Conclusions

Athletic trainers need to educate athletes with respect to safe OTC analgesic use. Safe OTC analgesic use includes, but is not limited to, knowing the recommended doses and dosing intervals and the potential adverse effects. The best advice is to strictly follow the package labeling and to know which other OTC medication may contain similar active ingredients. Acetaminophen is the safest OTC analgesic at therapeutic doses for alcoholics and for athletes who drink alcohol. Aspirin and NSAIDs can cause life-threatening GI bleeding and kidney damage, even at therapeutic doses. Trainers need to determine whether the anti-inflammatory benefits of NSAIDs outweigh the increased risks.

General Summary and Conclusions

Inflammation is an early physiologic response to injuries of soft tissue and bone and one that is necessary for healing to occur. A large body of clinical data suggests that chronic tendon injuries are not characterized by inflammation. These considerations raise the question of whether the anti-inflammatory effects of NSAIDs are desirable in the treatment of sports injuries. The risk of side effects from NSAIDs, even when taken at recommended therapeutic doses, is another concern for their use by athletes, especially given the availability of acetaminophen, an OTC analgesic with little or no anti-inflammatory effect and a more favorable side effect profile.

References

1. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. *Am J Phys Med Rehabil*. 2002;81(11 suppl):S52-S69.
2. Best TM, Hunter KD. Muscle injury and repair. *Phys Med Rehabil Clin N Am.* 2000;11:251-266.
3. Almekinders LC. Anti-inflammatory treatment of muscular injuries in sport: an update of recent studies. *Sports Med.* 1999;28:383-388.
4. Cotran R, Kumar V, Robbins S, eds. *Pathological Basis of Disease.* 6th ed. Philadelphia, Pa: Saunders; 1999.
5. Leadbetter W, Buckwalter J, Gordon S, eds. *Sports-Induced Inflammation.* Park Ridge, Ill: American Academy of Orthopedic Surgery; 1990.
6. Almekinders LC, Temple JD. Etiology, diagnosis, and treatment of tendonitis: an analysis of the literature. *Med Sci Sports Exerc.* 1998;30:1183-1190.
7. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies: update and implications for clinical management. *Sports Med.* 1999;27:393-408.
8. Astrom M, Rausing A. Chronic Achilles tendinopathy: a survey of surgical and histopathologic findings. *Clin Orthop.* 1995;316: 151-164.
9. Khan KM, Cook JL, Taunton JE, Bonar F. Overuse tendinosis, not tendinitis: part 1: a new paradigm for a difficult clinical problem. *Phys Sportsmed.* 2000;28:38-48.
10. Uhthoff HK, Sano H. Pathology of failure of the rotator cuff tendon. *Orthop Clin North Am.* 1997;28:31-41.
11. Alfredson H, Pietila T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med.* 1998;26:360-366.
12. Mafi N, Lorentzon R, Alfredson H. Superior short-term results with eccentric calf muscle training compared to concentric training in a randomized prospective multicenter study on patients with chronic Achilles tendinosis. *Knee Surg Sports Traumatol Arthrosc.* 2001;9:42-47.
13. Almekinders LC. The efficacy of nonsteroidal anti-inflammatory drugs in the treatment of ligament injuries. *Sports Med.* 1990;9:137-142.
14. Ogilvie-Harris DJ, Gilbart M. Treatment modalities for soft tissue injuries of the ankle: a critical review. *Clin J Sport Med.* 1995;5:175-186.
15. Frank CB. Ligament healing: current knowledge and clinical applications. *J Am Acad Orthop Surg*. 1996;4:74-83.
16. Reynolds JF, Noakes TD, Schwellnus MP, Windt A, Bowerbank P. Non-steroidal anti-inflammatory drugs fail to enhance healing of acute hamstring injuries treated with physiotherapy. *S Afr Med J.* 1995;85:517-522.
17. Beiner JM, Jokl P. Muscle contusion injuries: current treatment options. *J Am Acad Orthop Surg*. 2001;9:227-237.
18. Spitz DJ, Newberg AH. Imaging of stress fractures in the athlete. *Radiol Clin N Am*. 2002;40:313-331.
19. Zhang X, Schwarz EM, Young DA, Puzas JE, Rosier RN, O'Keefe RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair. *J Clin Invest*. 2002;109:1405-1415.
20. Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. *J Bone Miner Res*. 2002;17:963-976.
21. Perron AD, Brady WJ, Keats TA. Principles of stress fracture management: the whys and hows of an increasingly common injury. *Postgrad Med*. 2001;110:115-124.
22. Meyer SA, Saltzman CL, Albright JP. Stress fractures of the foot and leg. *Clin Sports Med.* 1993;12:395-413.
23. Hulkko A, Orava S. Stress fractures in athletes. *Int J Sports Med.* 1987;8:221-226.
24. Knapp TP, Garrett WE Jr. Stress fractures: general concepts. *Clin Sports Med*. 1997;16:339-356.
25. Einhorn TA. Do inhibitors of cyclooxygenase-2 impair bone healing? *J Bone Miner Res*. 2002;17:977-978.
26. Long J, Lewis S, Kuklo T, Zhu Y, Riew KD. The effect of cyclooxygenase-2 inhibitors on spinal fusion. *J Bone Joint Surg Am*. 2002;84-A:1763-1768.
27. Goodman S, Ma T, Trindade M, et al. COX-2 selective NSAID decreases bone ingrowth in vivo. *J Orthop Res*. 2002;20:1164-1169.
28. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis: the influence of reaming and non-steroidal anti-inflammatory drugs. *J Bone Joint Surg [Br]*. 2000;82:655-658.
29. *Physicians' Desk Reference®*. 56th ed. Montvale, NJ: Medical Economics Company, Inc; 2002.
30. National Council on Patient Information and Education (NCPIE). Available at http://www.bemedwise.org/survey/summary_ survey.pdf. Accessed July 29, 2003.
31. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340:1888-1899.
32. Kuffner EK, Dart RC, Bogdan GM, Hill RE, Casper E, Darton L. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med.* 2001;161:2247-2252.
33. Blot WJ, McLaughlin JK. Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. *J Epidemiol Biostat*. 2000;5:137-142.
34. Kaufman DW, Kelly JP, Wiholm BE, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *Am J Gastroenterol*. 1999;94:3189-3196.