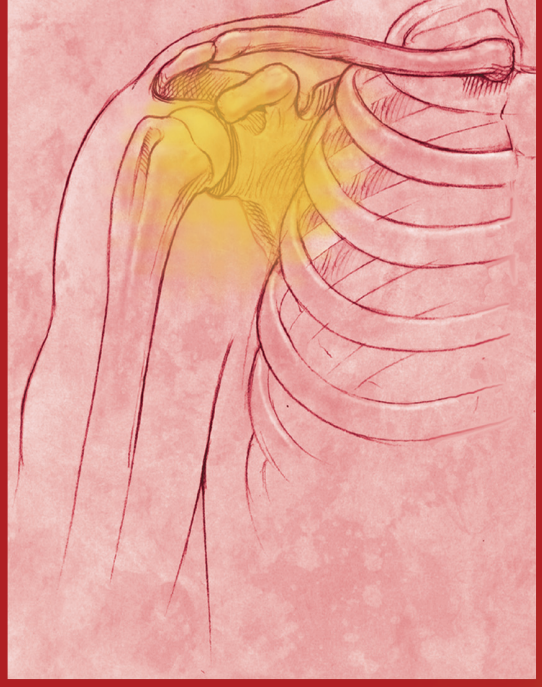
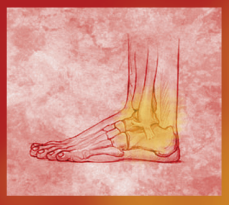


Includes Late Breaking FDA Recommendations

State-of-the-Art Management of Mild-to-Moderate Pain



Musculoskeletal Injuries and Analgesia

Presented by
The US Department of Health and Human Services
Office on Women's Health

In cooperation with

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Musculoskeletal Injuries and Analgesia reports highlights from a roundtable meeting presented by the US Department of Health and Human Services Office on Women's Health, under the auspices of the University of Colorado School of Medicine, and in cooperation with the American Pharmacists Association, the American Academy of Nurse Practitioners, and the American Academy of Physician Assistants.

This material is based upon a review of multiple sources of information, but is not exhaustive of the subject matter. Healthcare professionals and other individuals should review and consider other publications and material about the subject and not rely solely upon the information contained within this publication.

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Release Date: April 2005 Expiration Date: April 30, 2006

MUSCULOSKELETAL INJURIES AND ANALGESIA

INTRODUCTION

One of every 4 people in the United States suffers from a musculoskeletal injury or disorder.[1] The epidemic proportions of these disorders are reflected in annual direct and indirect costs of $254 billion, 147 million lost workdays, and 21 million lost school days. Musculoskeletal impairment causes approximately 153 million bedridden days among afflicted individuals and is now the number one reason for physician visits.[1,2] As the population ages, the magnitude of the problem is expected to grow accordingly. Indeed, the number of physician visits for symptoms related to the musculoskeletal system increased from nearly 79,600 visits in the year 2000 to more than 90,400 visits in 2001.[2,3] In recognition of the worldwide impact of musculoskeletal conditions on health, quality of life, and economics, the years 2001 to 2010 have been declared the Bone and Joint Decade by a coalition of the United Nations, World Health Organization, and 22 countries[1] and the Decade of Pain Control and Research by the US Congress.[4]

Musculoskeletal impairment… is now the number one reason for physician visits.

Musculoskeletal conditions embrace a broad array of diseases and injuries. The focus of this newsletter is pain management for soft tissue injuries. These occur in a number of settings and include overuse injuries as well as strains, sprains, and fracture-related damage. Although pain resulting from a tissue injury may be adaptive in helping protect injured tissues, it may also retard rehabilitation during the recovery process. From the perspective of the injured patient, pain is likely to be the overriding initial concern, and prompt intervention is crucial to its management.

INTENDED AUDIENCE

Healthcare Professionals

LEARNING OBJECTIVES

After reading this newsletter, the healthcare professional should be able to:

- Differentiate between the pathophysiologies of various musculoskeletal injuries
- Evaluate the role of inflammation in various musculoskeletal injuries
- Assess practical approaches for healthcare providers to manage mild-to-moderate pain associated with musculoskeletal injuries
- Educate patients on the safe and optimal use of over-the-counter (OTC) pain medications for treating mild-to-moderate pain associated with musculoskeletal injuries

LATE BREAKING NEWS FROM FDA AS OF APRIL 7, 2005:

- FDA has asked Pfizer, Inc. to withdraw Bextra® (valdecoxib) from the market because the overall risk versus benefit profile for the drug is unfavorable. FDA has also asked Pfizer to include a boxed warning in the Celebrex® (celecoxib) label.
- FDA is asking manufacturers of all other prescription NSAIDs to revise their labels to include the same boxed warning highlighting the potential for increased risk of cardiovascular (CV) events and gastrointestinal (GI) bleeding associated with their use.
- FDA is asking the manufacturers of all OTC NSAIDs to revise their labels to include more specific information about the potential CV and GI risks, and information to assist consumers in the safe use of the drugs. FDA is also asking manufacturers of OTC NSAIDs to include a warning about potential skin reactions.

New evidence on the physiology of injury and the complex role of inflammation in healing has provided impetus for a reassessment of standard approaches to pain management associated with musculoskeletal injury. Traditionally, anti-inflammatory agents such as aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to treat these injuries, but leading experts suggest that this practice may need to be reconsidered. Based on increasing knowledge about the pathophysiology of musculoskeletal injury, evolving treatment strategies may help expedite healing and return of function.

Recently, experts in pain management met under the auspices of the US Department of Health and Human Services Office on Women's Health to examine the impact of mild-to-moderate pain, including pain from musculoskeletal conditions, on individuals, society, and the healthcare system, and to present and discuss information for educational initiatives designed to help improve clinical outcomes. This issue of *Clinical Courier*® presents key information that was presented on the management of mild-to-moderate pain in several types of soft tissue injury.

INJURY AND HEALING: THE CONJUNCTION OF BASIC SCIENCE AND CLINICAL APPLICATION

Not all musculoskeletal injuries share the same underlying pathophysiology, thus they often heal differently. The type of injury has a great deal of influence over wound healing,[5] and, by extension, the type of injury may have a considerable influence on its management.

Sports injuries provide good models for the various pathophysiologies that can arise in musculoskeletal injuries. Specifically, mechanisms of injury in sprains (ligament injuries) and strains (muscle/tendon damage due to partial tears and direct contusions) differ from tendinopathies as well as from delayed-onset muscle soreness (DOMS). Therefore, it is necessary for the clinician to consider the type of injury when deciding how best to manage the patient.

Strains, Sprains, and Fracture-Associated Damage

The body's response to injuries such as strains, sprains, and tissue damage associated with fracture follows a predictable sequence of events that comprise 3 overlapping phases, each of which is essential to the subsequent phase: acute inflammation, proliferation, and maturation.[6-8]

The Inflammatory Phase. Inflammation sets the stage for all other events involved in the healing process. It can and should be viewed as a localized, protective tissue response that helps isolate injured tissue and destroy damaging cellular by-products or injurious agents.[9] This initial response of vascularized tissue to injury lasts up to 7 days, depending on the specifics of the injury.[8] A clinically based schema of sports-induced inflammation from strain and overuse is depicted in Figure 1.[10] Macro- or microtrauma results in tissue overload and mechanical strain and stress. The stress response occurring in the cell matrix, although painful, is thought to be reversible depending upon the subsequent tissue load. When the load on the tissue is optimal, spontaneous resolution of symptoms may occur. Alternatively, when an abusive load is continued in the absence of major structural or vascular damage, cell atrophy and degenerative changes are possible.[10] When the abusive load is continued and is associated with structural and vascular disruption, further damage and continued inflammation can result in muscle cell death and irreversible tissue damage.[10] This complex inflammatory response comprises a number of events,[8] including:

- Tissue edema
- Exudation of fibrin
- Infiltration of inflammatory cells (leukocytes, monocyte–lymphocyte line cells, macrophages)
- Production of fibronectin
- Thickening of capillary walls
- Occlusion of capillaries

As a result of the inflammatory responses, cytokines and other growth factors (GFs) are directed to the injury.[6] Part of this process is mediated by prostaglandins, which are formed from arachidonic acid by the dual cyclooxygenase (COX) pathways, COX-1 and COX-2 (Figure 2).[6]

FIGURE 1[10]

THEORETICAL PATHWAYS OF SPORTS-INDUCED INFLAMMATION

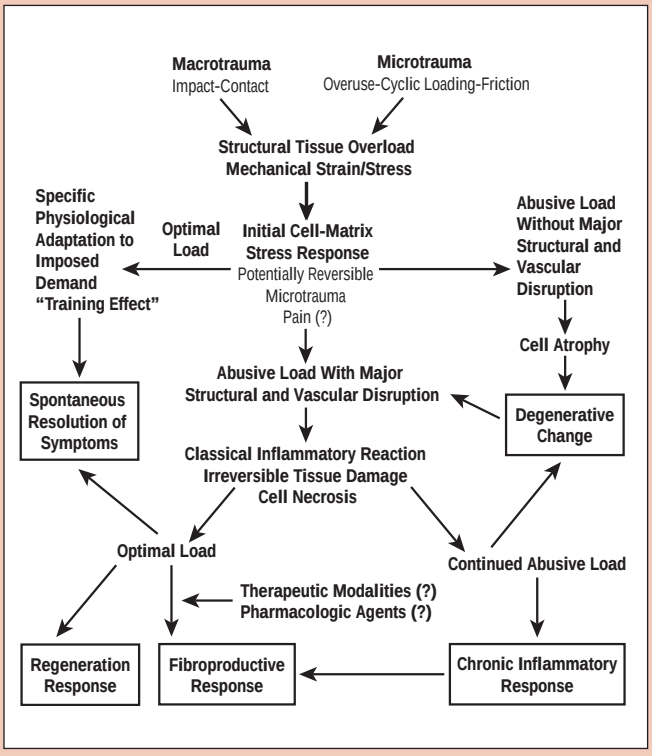

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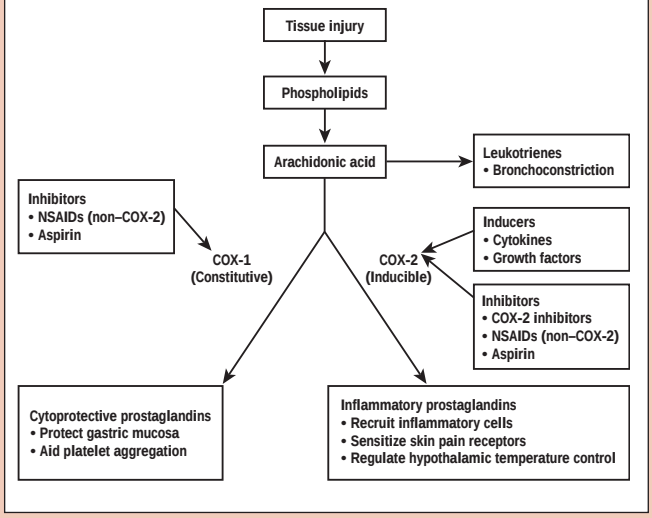
FIGURE 2[6]

FORMATION OF PROSTAGLANDINS IN TISSUE INJURY



NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.
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The clinical counterparts of inflammation are the 4 cardinal signs first described by Celsus (AD 14-37): swelling, erythema, increased temperature, and pain.[5,9] In addition, function is disrupted.[9] The recruited vascular, cellular, and chemical mediators eventually lead to tissue regeneration and repair. In some settings, excessive inflammation and chronic degeneration occur along with scar and adhesion formation.[8] The circumstances under which an injury evolves to a chronic inflammatory condition are poorly defined, but research suggests that continued abuse and irritation may stimulate local cytokine release that prolongs cellular activity. Deviation from the normal healing progression in a wound can lead to granulation tissue formation or tissue degeneration.[9]

The Proliferative Phase. This phase, which takes place approximately 7 to 21 days post injury, is characterized by fibrin clotting and macrophage- and GF-induced migration and proliferation of fibroblasts, myofibroblasts, synovial cells, and capillaries.[8] Phagocytic processes eliminate damaged

material, and the production of fibronectin, collagens, and the proteoglycans and glycoproteins of the extracellular matrix increase. As the proliferation phase proceeds, granulation tissue gradually replaces the original fibrin clot.

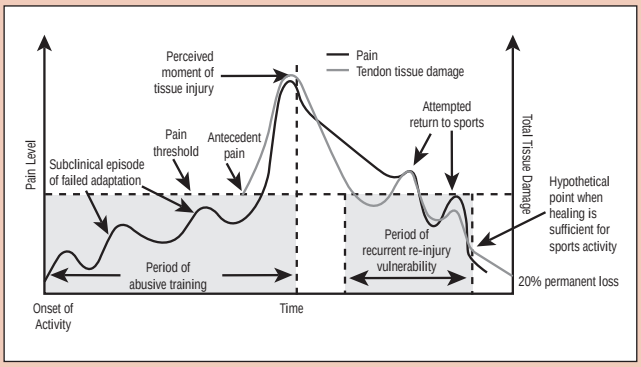
The Maturation (Remodeling) Phase. Fibroblasts continue building the new extracellular matrix.[6] As maturation continues, the proteoglycan-water, cell, and capillary content of the tissue decreases, and, simultaneously, Type I collagen (basic collagen of musculoskeletal tissues) begins to orient normally and eventually is able to withstand stress. This stress resistance may be observed by about 6 to 8 weeks after the injury, but complete healing can take 1 to 2 years.[8]

Other Injuries

Tendon Injuries. Chronic tendon disorders, commonly due to overuse, are frequently given the misnomer "tendinitis." Although the suffix "itis" connotates the presence of inflammation, research has consistently failed to show the presence of inflammatory cells within the injured tissue.[11,12] Rather, the histopathology of overuse tendon conditions is typically consistent with tendinosis, a degenerative state associated with chronic, microtraumatic injury but without clinical or histologic evidence of inflammation.[5,11] Furthermore, acute injuries may be the result of pre-existing tissue damage, a sequence of events illustrated in Figure 3.[5,11,13] For example, an athlete might complain of elbow pain after lifting a bag of groceries, but there is really no way to determine whether this is an acute injury or simply the result of pre-existing tendon damage.

FIGURE 3[5]

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.

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There have been no human studies that have definitively demonstrated true tendinitis, which would involve inflammation, although the condition reportedly has been observed in rabbits.[12] Although tendon-associated inflammation may occur in some settings, the vast majority of tendinopathies treated clinically are likely to be chronic and are therefore more accurately termed tendinosis.[11]

Delayed-Onset Muscle Soreness. Occurring after repeated eccentric exercise that causes elongation and simultaneous contraction of the muscle, DOMS is muscle soreness and decreased function that occurs approximately 24 to 48 hours after the activity.[7,14] The pathophysiology of DOMS is less defined than that of other soft tissue injuries such as strains and sprains, but appears to differ in several respects.[7] First, any inflammatory response that occurs is limited and fails to correlate with clinical symptoms. Fibroblast activation also has not been observed. Under electron microscopy, damage to sarcomere subunits within muscle fibers has been seen. In addition, evidence of structural damage is reflected in elevated plasma levels of plasma creatine kinase (CK).[7] At least 6 theories have been proposed to account for DOMS.[14] Consensus holds that a full explanation is likely to include elements of each theory, such as damage to connective tissues and muscles, enzyme efflux, and inflammation,[14] which may ultimately have treatment implications as discussed below.

Clinical Implications of Injury: Pathophysiology, Inflammation, and Healing

Inflammation may not be present in all injuries that are accompanied by pain, and/or the role of inflammation is unclear in certain injuries. When inflammation is the result of tissue injury, animal data indicate that anti-inflammatory agents may actually retard healing.[15] Proper analgesia, however, is important because it enables the patient to heal and participate in a conditioning program that is important for a full recovery.[16]

The pain of musculoskeletal injury usually necessitates prompt treatment. Information on the pathophysiology of these injuries suggests that selecting the most appropriate agent should be based on several key principles, including:

- Making an accurate diagnosis; the various conditions do not necessarily share the same pathophysiology and may require different treatment plans
- Distinguishing the injury itself from the pain component
- Developing treatment strategies that address pain and injury as separate, albeit related, clinical issues
- Considering the potential side effects of treatment and their impact on healing when making treatment decisions

By reducing suffering and discomfort, analgesia may facilitate a more rapid rehabilitation.

ANALGESICS

The management of mild-to-moderate pain in musculoskeletal injury, particularly in sports medicine, has been dominated historically by the use of NSAIDs, in part because of the misperception that inflammation is always involved in injury and that its effects are deleterious.[6] Like NSAIDs, acetaminophen has both analgesic and antipyretic properties. In contrast to them, however, acetaminophen does not have anti-inflammatory activity.

Analgesic Mechanisms of NSAIDs

Analgesic and anti-inflammatory properties of NSAIDs are mediated primarily through inhibition of the COX enzyme, which catalyzes the conversion of arachidonic acid into a number of compounds, including prostaglandins and thromboxanes that are involved in normal physiologic functions and inflammation. The COX enzyme exists in 2 isoforms, COX-1 and COX-2, which perform different functions in different tissues.[17-20] Nonselective NSAIDs block the activity of both isoforms. COX-1 mediates prostaglandins that maintain the integrity of the gastrointestinal (GI), renal, and vascular mucosa and protect surface epithelial cells. COX-2 induces pro-inflammatory prostaglandins, which cause the stiffness, swelling, and pain that accompany an illness or injury. Thus, COX-1 inhibition leads to adverse GI and antiplatelet effects, while the inhibition of COX-2 may account for NSAIDs' interruption of the inflammatory process.

Analgesic Mechanisms of Acetaminophen

The analgesic mechanism of acetaminophen has not been fully elucidated; however, the drug is believed to increase the pain threshold within the brain.[21] Acetaminophen has minimal inhibitory effects on prostaglandin synthesis, which may be greater in the central nervous system than in the periphery.[22] The analgesic potency of acetaminophen is similar to that of aspirin, and the drug is devoid of anti-inflammatory effects.

COX-1 inhibition leads to adverse GI and antiplatelet effects, while the inhibition of COX-2 may account for NSAIDs' interruption of the inflammatory process.

PHARMACOLOGIC AND NONPHARMACOLOGIC MANAGEMENT OF STRAINS, SPRAINS, AND FRACTURE-ASSOCIATED SOFT TISSUE INJURY

Soft tissue injuries are traditionally handled by rest, ice, compression, and elevation (RICE). Although well accepted, the efficacy of RICE has not been rigorously examined in controlled clinical trials.

Rest and immobilization, which are suitable to help alleviate initial pain and prevent re-injury, may ultimately be detrimental to healing if continued beyond the acute phase of injury. Extended immobilization can result in tissue atrophy, whereas controlled muscle stretching and joint movement may improve collagen fiber orientation to parallel the stress lines of normal fibers.[8] With fractures, mechanical load ultimately stimulates the bone remodeling process; therefore, mobilization is desired after the initial acute phase of injury. *Ice* can relieve pain by affecting nerves and causing temporary vasoconstriction to reduce edema, but its ultimate effects on swelling are unclear. *Compression* decreases swelling, but the effects on pain and outcome have not been clarified. In one study, time to recovery did not differ between patients receiving immediate compression and those who did not.[23] In fractures, compression may cause neurovascular complications. Finally, *elevation* is logical initially because it may alleviate swelling by counteracting gravitational effects and improving venous return, but there are no data on its benefits.

Pharmacologic options for pain management include prescription and nonprescription analgesics. When pain is mild-to-moderate in severity, choices include selective and nonselective NSAIDs and acetaminophen. However, few placebo-controlled or comparative trials of these medications have systematically examined their efficacy and safety.

Analgesia in Ligament and Muscle Injuries

NSAIDs. In 1990, Almekinders identified more than 35 articles on the efficacy of NSAIDs in sprains and strains, but only 15 met criteria that allowed valid conclusions.[24] There were few differences among various NSAIDs unless they were being compared with placebo. Moreover, it was not possible to determine if treatment influenced outcome because injuries tend to improve over time. Of the 15 studies that included a placebo control, only 8 (6 knee, 2 ankle) evaluated a single ligamentous injury. The results of 4 of the 8 studies showed a significantly better outcome for treatment versus placebo. For all 15 studies, regardless of the type of injury, the findings of 9 studies provided some evidence of NSAID benefit. Dosing was not well specified, and outcome measures were usually subjective, which could have made it difficult to detect benefits.

In a more recent review of the literature, Almekinders concluded that NSAIDs do not appear to offer major benefits for soft tissue injuries.[12] Additionally, the findings of a randomized controlled trial on hamstring tears indicated that in patients with severe pain, those receiving placebo had significantly lower pain scores at Day 7 ($P=.05$) than did those receiving the prescription NSAIDs diclofenac or meclofenamate.[25] In patients with less severe pain, no differences among groups were observed.

Acetaminophen. No placebo-controlled trials on the efficacy of acetaminophen in sprains have been published. However, the comparative efficacy of acetaminophen, rofecoxib, and placebo were examined in a mouse model of nonpenetrating muscle injury.[26] The group receiving placebo had more gait disturbances at day 2 than did the active treatment groups ($P<.05$), but no other differences were observed. The investigators concluded that the outcome differences were not due to anti-inflammatory effects, which were similar in all groups.

Clinical Issues: Analgesics and Healing in Strains, Sprains, and Fracture-Associated Injury. Based on their mechanisms of action, NSAIDs may diminish the inflammatory response at prescription doses and retard healing.[7] Almekinders and Gilbert found that NSAIDs caused a delay in anti-inflammatory response and muscle regeneration soon after injury in an animal model (rat tibialis anterior muscle) of experimental muscle strain.[27] While animal data cannot necessarily be extrapolated to humans, the results suggest that although NSAIDs may initially produce pain relief, they may also result in some small deleterious effects during recovery.[7] However, additional studies in humans are needed.

In another experimental study, the effect of piroxicam versus no treatment on controlled muscle strain injury was investigated in rabbits.[28] Muscle function, tensile strength, and histology were assessed. In the piroxicam-treated rabbits, muscle contractile force was greater in treated than in untreated rabbits at Day 1, but at no other time period. Tensile strength was unaffected by treatment. Histologic findings, however, revealed delayed degradation of damaged tissue and slower regeneration of muscle tissue in the piroxicam-treated group. Again, animal data cannot necessarily be extrapolated to humans, therefore the clinical significance of these findings has not been evaluated.

Although NSAIDs may initially produce pain relief, they may also result in some small deleterious effects during recovery.

The COX-2–selective NSAID celecoxib was investigated in an animal model of acute ligament injury and healing.[15] After surgical ligament injury, rats were given celecoxib or no treatment. In a mechanical test of ligament failure, celecoxib-treated ligaments failed at a 32% lower load than did untreated ligaments. The authors concluded that the results do not support the use of COX-2–specific NSAIDs to treat ligament injuries, however, additional studies in humans are needed.

In fractures, soft tissue trauma and inflammation contribute to pain. Adequate pain control is important for patient well-being and to ensure that rehabilitation can be undertaken as soon as possible to achieve optimal healing. Therefore, analgesia is required for all levels of pain. Without pain control, the patient may be unwilling to bear weight, which is necessary for tissue repair. Initially, opioids and opioid/acetaminophen combinations can be used along with immobilization and surgery when it is deemed necessary, but other analgesics may be necessary as the healing process continues.

Clinical Issues: Analgesics and Healing in Bone Injuries. Bone healing occurs in 4 phases: inflammation, proliferation, maturation, and callus formation. As in other musculoskeletal injuries, inflammation is a necessary response, as it protects the injured structure from further use, clears away cell and matrix debris, and may facilitate proliferation. COX-2, which is inhibited by both nonspecific NSAIDs and COX-2–specific NSAIDs, regulates inflammation and callus formation.[29,30]

The effect of NSAIDs on bone healing has been recently reviewed.[31] The results of both animal and in vitro studies showed that nonselective and COX-2–selective NSAIDs were detrimental to bone healing. In addition, the results of a retrospective analysis of patients with diaphysis fractures of the

REASSESSMENT OF THE RISK–BENEFIT PROFILE OF SELECTIVE AND NONSELECTIVE NSAIDs

On September 30, 2004, Merck & Co., Inc., voluntarily withdrew rofecoxib, a selective inhibitor of cyclooxygenase-2 (COX-2), from the market after preliminary data from its most recent trial, Adenomatous Polyp Prevention on Vioxx (APPROVe), demonstrated an increased risk of myocardial infarction (MI) and stroke. In this trial of 2600 patients with colon polyps and no history of cardiovascular (CV) disease, it was discovered that 3.5% of rofecoxib-treated patients had experienced MI or stroke, compared with 1.9% of placebo-treated patients (P<.001).[1]

More recently, it has been reported that 2 other coxibs, valdecoxib and celecoxib, as well as the over-the-counter nonselective nonsteroidal anti-inflammatory drug (NSAID) naproxen have been associated with an increased risk of CV events, which underscores the urgency in determining if the CV effects of rofecoxib are actually a class effect for all selective and nonselective NSAIDs.

The need for an NSAID with an improved gastrointestinal (GI) safety profile led to the development of COX-2 inhibitors, which are purported to selectively inhibit the enzymes responsible for synthesizing the prostaglandins that induce inflammation and cause pain, while sparing COX-1 enzymes, which are not associated with adverse GI effects.

In 2000, Bombardier and colleagues first identified the potential for an increased risk of CV events with rofecoxib use in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, which compared the GI toxicity of rofecoxib with that of naproxen, a nonselective inhibitor.[2] Although not designed to assess CV events, investigators found a 4-fold increase in the incidence of MI associated with rofecoxib. In the following year, Mukherjee and colleagues analyzed CV event data from the VIGOR and the Celecoxib Long-term Arthritis Safety Study (CLASS) trials, as well as 2 smaller trials.[3] In their review of the CLASS data, they found no significant difference in CV event rates between celecoxib and NSAIDs; however, the annualized MI rates for COX-2 inhibitors in both VIGOR and CLASS were significantly higher than those found in the placebo group of a recent meta-analysis of 23,407 patients in primary prevention trials: 0.74% with rofecoxib (P=.04) and 0.80% with celecoxib (P=.02).

Although the FDA implemented labeling changes in 2002 to reflect safety results in the VIGOR trial, Merck & Co., Inc., responded by proposing that the explanation for differences in MI rates between rofecoxib and naproxen were due to the cardioprotective effect of naproxen, a theory that has been reiterated in 3 case-control studies.[4-6] However, a much larger, more rigorous cohort study by Ray and colleagues found no protective effect of naproxen or other nonaspirin NSAIDs on the risk of coronary heart disease.[7] On the contrary, an Alzheimer's disease prevention trial was recently suspended after 3 years when researchers found that patients taking naproxen had a 50% greater incidence of heart attack or stroke than patients taking placebo.[8] As this is the first study to show that naproxen might increase the risk of heart attack or stroke, and because other studies have supported a modest degree of cardioprotection, it seems premature to judge any possible untoward cardiovascular effect of naproxen.[9] However, until further studies are complete, it is important to remember that naproxen use is not recommended for more than 10 days,[8] and patients should be counseled about the risks of exceeding the recommended dosing and duration of therapy for all analgesics.

Although further study is necessary to determine the exact relationship between NSAID use and CV events, currently there are more questions than answers. As physicians consider how to counsel patients who take selective and nonselective NSAIDs, more and more safety concerns are emerging for these analgesics. For example, a recent study demonstrated that the risk of acute MI is actually increased during several weeks after the cessation of NSAID therapy.[10] The reality is that many patients must continue to take analgesics over the long term. Because of the lack of definitive safety profiles for NSAIDs, it is important to carefully evaluate each patient's relative CV risks profile before prescribing or discontinuing NSAID therapy, and to consider other analgesics with better established safety profiles, if appropriate.

Since the withdrawal of rofecoxib from the market, the manufacturer of valdecoxib has announced the results of a study that demonstrated an increased risk of heart attack, stroke, and blood clots in heart bypass surgery patients taking valdecoxib. Furthermore, the National Institutes of Health announced that the use of celecoxib has been suspended in a large colorectal cancer prevention clinical trial because an independent analysis by the Data Safety and Monitoring Board showed a 2.5-fold increased risk of major fatal and nonfatal CV events for patients taking high doses of celecoxib (400 mg/d) versus placebo, and a 3.4-fold increase in those patients taking 800 mg/d versus placebo.[11,12] Although further study is necessary to determine the CV effects of these agents more definitively, the possibility that these agents have negative CV effects is not new. In 1999, Fitzgerald and colleagues first found evidence that all COX-2 inhibitors could theoretically cause CV events.[13] Nonselective NSAIDs reduce the formation of thromboxane A_2, which increases platelet aggregation, and prostaglandin I_2, which is a potent vasodilator and inhibits platelet aggregation. COX-2–selective agents also inhibit the production of prostaglandin I_2, but have no effect on thromboxane A_2, which may upset the balance between COX-1 and COX-2 isoforms and platelet inhibition and activity. This imbalance could potentially increase platelet aggregation and predispose patients to MI or thrombotic stroke.[13]

There have also been reports demonstrating that COX-2–selective inhibitors may have adverse cardiorenal effects. The Successive Celecoxib Efficacy and Safety Study VI (SUCCESS VI) showed that rofecoxib and celecoxib increased systolic blood pressure in 17% and 11% of patients, respectively, and increased edema in 9.5% and 4.9% of patients, respectively.[14] Other evidence has shown that COX-2 inhibitors impair renal function and cause sodium retention in patients with mild pre-existing renal failure and, potentially, in elderly patients with, for example, volume depletion.[15]

In addition to the possible CV and cardiorenal class effects of COX-2 inhibitors, valdecoxib labeling had been updated to include a black box warning regarding the risk of Stevens-Johnson Syndrome, a rare, serious, and potentially fatal skin reaction. Although this is a rare adverse event, the risk of this skin reaction is reportedly greater than with other COX-2–specific products, such as celecoxib.[16]

In light of the recent withdrawal of rofecoxib and valdecoxib, and reports linking celecoxib and naproxen to an increased risk of CV events, there is a need for greater scrutiny of all NSAIDs. With this in mind, Muhammed Mamdani, PharmD, has proposed the following stepwise approach to pain management.[17] Acetaminophen, which is not associated with significant CV or cardiorenal effects,[18,19] as the first-line agent for mild-to-moderate pain. Ibuprofen is recommended for those patients who do not respond to the maximum recommended dose of acetaminophen (4000 mg/d), and are not at risk for heart disease,[18] kidney disease,[19] or GI side effects.[20] Although COX-2 inhibitors remain a rational choice for patients at high risk for GI events who are at low risk for CV events, it would seem sensible to avoid prescribing these agents to patients who have or are at risk for CV events until further long-term studies are complete. Furthermore, the cost of these agents may be prohibitive for some patients, and their potential clinical benefit must be assessed in light of their added expense. The withdrawal of rofecoxib and valdecoxib from the market, and the suggested labeling revisions for celecoxib and both OTC and prescription NSAIDs have created more questions about the safety profiles of these drugs and shifted the onus of proof on the manufacturers of these agents. Clear evidence about the safety and efficacy of selective and nonselective NSAIDs is needed before confidence in these classes of drugs can be restored.

The FDA Arthritis and Drug Safety Advisory Committee conducted a systematic review of NSAID-related safety issues on February 16-18, 2005. See page 1 for late breaking news from FDA.

femur showed that there was a highly significant (P=.000001) association between nonunion of the fracture and the use of NSAIDs after injury.[32]

. . .nonopioid analgesic options that do not inhibit inflammation may be a better choice for mild-to-moderate pain associated with fractures, as they would not be expected to interfere with bone healing.

Moreover, NSAID treatment also delayed healing in patients whose fractures had united. Studies are warranted to determine if similar inhibitory effects of NSAIDs on bone healing occur in clinical settings. Although the efficacy of acetaminophen alone in acute fracture pain has not been documented, nonopioid analgesic options that do not inhibit inflammation may be a better choice for mild-to-moderate pain associated with fractures, as they would not be expected to interfere with bone healing.

Clinical Issues: Analgesics and Muscle Function in DOMS

The role of common analgesics in DOMS remains unclear. As discussed, the pathophysiology appears to be complex and involve a number of components.[14] The results of studies investigating the efficacy of NSAIDs in DOMS are conflicting, but many of them indicate a lack of significant benefit for treating muscle soreness.[7,14] In these studies, type, dose, and timing of medication varied quite considerably, which could account for some of the findings.[14]

A comparison of ibuprofen with acetaminophen did not reveal any anti-inflammatory effects of either agent, as evidenced by neutrophil or macrophage concentrations after eccentric exercise versus placebo.[33] In another study, however, both ibuprofen and acetaminophen suppressed the normal increase in prostaglandin $F_{2\alpha}$ and protein synthesis that occurs after eccentric resistance exercise.[34,35] In this study, 24 patients were randomized to receive acetaminophen (4000 mg/d), ibuprofen (1200 mg/d), or placebo, beginning treatment at the start of a period of high-intensity eccentric exercise.[35] There were no differences in the level of perceived muscle soreness among the 3 groups at any time point. Taken together, the results of these studies suggest the need for well-controlled comparative trials of adequate therapeutic doses of common analgesics designed to evaluate biochemical and clinical endpoints in DOMS.

Clinical Issues: Analgesia and Management of Tendon Injuries. NSAIDs have been used extensively for the treatment of tendon injuries based on the assumption of an inflammatory component to the injury. However, available clinical data fail to support this assumption. According to a comprehensive review of the literature, of 32 studies published on the use of NSAIDs in tendon injuries, only 9 were prospective and placebo-controlled.[12] The results of 5 of these studies showed improvement in pain scores with the NSAID, but follow-up ranged from only 7 to 28 days. Because the data on tendon injuries suggest that complete recovery may take several months, the impact of NSAID treatment on healing could not be adequately assessed after the relatively brief follow-up in the controlled trials.

When tendinosis is the diagnosis, several implications for management must be considered. Recovery time is likely to be prolonged regardless of whether clinical presentation occurs early or late in the injury.[13] An important focus of treatment is the encouragement of collagen synthesis and maturation. Controlled physical therapy may provide significant benefit. For example, eccentric calf muscle training with a physical therapist appears to reduce pain associated with Achilles tendinosis, build strength, and permit patients to resume normal activities.[16,36] The precise mechanisms whereby these exercises improved tendinopathies is unknown. Researchers proposed that remodeling of the tendon may result from eccentric loading or from changes in the tendon resulting in altered pain perception.[16,36] More specifically, exercise may result in collagen production by stimulating mechanoreceptors in tenocytes.[13] Results of studies in animals reveal that tendon loading improves alignment of collagen as well as stimulating cross-linkage of collagen, both of which enhance tensile strength. Within this context of rehabilitation, analgesics may be important in providing pain relief sufficient to promote active participation in the recovery process.

Considerations in Selecting an Analgesic

In selecting a specific medication, overall risks and benefits should be considered with each medication. Despite the large variety of pain medications available in the United States, over-the-counter (OTC) agents contain only 5 active analgesic ingredients: acetaminophen, aspirin, ibuprofen, ketoprofen, and naproxen sodium. These 5 therapeutic entities are available for oral, nonprescription analgesia either alone or in combination products. Although these agents play a fundamental role in pain management, the appropriate use of these agents could be improved. Consumers often neglect to read product labels, or are poorly informed about safe dosing, which puts them at risk of overmedicating, with its subsequent adverse consequences. Table 1[37] reviews general counseling considerations that apply to each agent.

It is also important for patients to understand the side effects associated with prescription and OTC medications. Among the analgesic agents available for mild-to-moderate pain, nonselective NSAIDs as a class are associated with adverse GI effects. The estimated risk of GI bleeding with various analgesics is shown in Table 2.[38] Based on current data, it is clear that NSAIDs, even at OTC doses, are associated with both upper and lower GI risks.[39-41] Aspirin contributes substantially to this risk, even when it is used occasionally or at low doses.[42,43] Acetaminophen, because it has minimal effect on prostaglandin synthesis, is not associated with negative GI effects.[38]

While prescription COX-2 inhibitors are believed to have improved GI safety profiles, thought to result from their more selective effects, only rofecoxib has clearly established a proven GI benefit.[44] The Celecoxib Long-term Arthritis Safety Study (CLASS), which compared celecoxib 400 mg bid, ibuprofen 800 mg tid, and diclofenac 75 mg bid (aspirin use for cardiovascular prophylaxis was permitted), demonstrated that there was a statistically insignificant reduction in upper GI events after using celecoxib after 6 months.[45] However, there was no clear difference with celecoxib in the risk of GI complications at 12 months follow-up and in patients taking aspirin therapy.[46] Although these agents are more expensive than traditional NSAIDs and acetaminophen, their putative beneficial effects on the GI tract were thought to improve their cost-effectiveness in patients at high risk for GI effects.[47] However, comparing the safety profiles of available analgesics has been further complicated by the recent withdrawal of rofecoxib and valdecoxib from the market due to their adverse cardiovascular event profiles, and the subsequent announcement by the manufacturers of celecoxib and the OTC nonselective NSAID naproxen that these agents may also be associated with negative cardiovascular effects.[48-50] (See page 5 for information on the reassessment of the risk-benefit profile of selective and nonselective NSAIDs.)

Although the analgesic efficacy of selective and nonselective NSAIDs have never been called into question, the recent findings regarding the cardiovascular safety of these drugs has placed NSAIDs under greater scrutiny while investigators strive to determine whether there is an adverse cardiovascular effect for this class of drugs. Until more definitive side-effect profiles are established for these agents, clinicians may want to consider reserving their use for patients with no risk factors for cardiovascular disease.

It is also important for patients to understand that all medications, including OTC drugs, can be associated with side effects. Patients may need to be reminded or educated that ingredients may be duplicated in various preparations, that they should read labels carefully, and that they should not exceed the maximum recommended daily doses.

TABLE 1[37]

NONPRESCRIPTION ANALGESIC AGENTS FOR ORAL USE

Categories/Properties	Products	General Counseling/Usage Issues*
Acetaminophen • **Analgesic** • **Antipyretic**		• Can be used in patients with GI distress, peptic ulcer disease, asthma, gout, allergy, or sensitivity to aspirin, and in children • Does not have anti-inflammatory effects • Consumers should be aware that dosing varies depending on dosage form (eg, tablet, gel cap, suspension)
NSAIDs • **Analgesic** • **Antipyretic** • **Anti-inflammatory**	**Aspirin** (acetylsalicylic acid; ASA)	• Take with milk, food, or full glass of water • Avoid lying down for 15-30 minutes after ingestion • Do not use if a strong vinegar odor is present • Notify physician if tinnitus, shortness of breath, or bleeding occurs • Be aware of the potential for drug interactions and speak to a healthcare professional • Avoid use in children because of the relationship between viral illness, Reye's Syndrome, and aspirin use • Avoid use if peptic ulcer disease is present
	Ibuprofen, Ketoprofen, Naproxen	• Take with milk, food, or full glass of water • Be aware of the potential for drowsiness or dizziness • Avoid use if peptic ulcer disease is present • Notify a physician in the event of weight gain, edema, rash, or bleeding because of the potential for GI intolerance, hematologic side effects, central nervous system side effects, and renal side effects • Products are not interchangeable, as half-lives vary

*Please see product labeling for detailed information on each specific product.
GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
Source: Engle JP. Nonprescription-pharmacologic approaches to managing mild-to-moderate pain. Presented at US Department of Health and Human Services State of the Art Management of Mild-to-Moderate Pain Closed Roundtable Meeting; December 10-11, 2003; Washington, DC.

TABLE 2[38]

GI BLEEDING ASSOCIATED WITH ANALGESICS

Analgesic	Case, % (n=627)	Control, % (n=590)	OR	95% CI
OTC use of				
Aspirin	27.0	12.0	2.7	1.9-3.8
Ibuprofen	10.1	5.8	2.4	1.5-3.9
Acetaminophen	4.5	6.3	0.9	0.5-1.6
Total OTC NSAIDs	36.2	17.5	3.0	2.2-4.1
Rx NSAIDs	9.3	5.9	2.1	1.2-3.4
Total NSAIDs	42.9	22.0	3.1	2.3-4.1

GI, gastrointestinal; OR, odds ratio; CI, confidence interval; OTC, over-the-counter; NSAID, nonsteroidal anti-inflammatory drug; Rx, prescription.

Reprinted with permission from Blot WJ, McLaughlin JK. *J Epidemiol Biostat.* 2000;5:137-142.

SUMMARY AND CONCLUSIONS

Pain is a common denominator in all musculoskeletal injuries and is likely to be the most important initial concern of patients. To optimally manage both the pain and the injury and thereby encourage healing, current data suggest the value of understanding the basic physiology of injury/healing and distinguishing the underlying injury from its associated pain. An examination of the growing body of literature on the pathophysiology of injury and healing demonstrates that injury and repair are a continuum of events that differ according to the type of injury. In strains, sprains, and fracture-associated tissue damage, inflammation is fundamental to the body's response to the injury and to initiation of the repair process. In contrast, inflammation appears to have little or no role in common tendon injuries, more appropriately referred to as tendinosis, not tendinitis. The pathophysiology of DOMS is less well understood, but current evidence suggests that inflammation is not a key component of the injury, although the evidence supporting this derives mainly from animal studies.

When inflammation is essential to healing, the use of analgesics with anti-inflammatory activity (eg, NSAIDs) may actually interfere with the healing process, as shown in a number of studies of muscle and ligament injury. Moreover, NSAIDs may retard bone healing in fractures. When prescribing an analgesic, it is also important to recognize that some agents are associated with cardiovascular, cardiorenal, and GI side effects. For the relief of mild-to-moderate pain in patients at risk for these adverse events, a simple analgesic such as acetaminophen may be a more appropriate choice.

In summary, the principles of managing musculoskeletal injury are to make an accurate diagnosis, distinguish the underlying problem from the associated pain, and treat each within the context of potential treatment side effects and impact on healing.

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Reassessment of the Risk–Benefit Profile of Selective and Nonselective NSAIDs

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Answer Key: 1.a, 2.b, 3.a, 4.c, 5.c, 6.b, 7.a, 8.b, 9.e, 10.e.

MUSCULOSKELETAL INJURIES AND ANALGESIA

Posttest Self-Assessment/CME Verification

If you wish to receive CME credit and confirmation of your participation, please mail a photocopy of this completed form before April 30, 2006, to:

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Instructions: For each of the questions or incomplete statements below, indicate the most appropriate response below.

1. In the United States, musculoskeletal injuries affect how many individuals annually?
   a. 1 of 4
   b. 1 of 6
   c. 1 of 10
   d. 1 of 15

2. In strains and sprains, the 3 phases of the body's response to injury include all but which one of the following?
   a. Inflammatory
   b. Degenerative
   c. Proliferative
   d. Maturation

3. In healing of tendon injuries, granulation tissue replaces the original fibrin clot during the proliferation phase. True or False?
   a. True
   b. False

4. In soft tissue injury, the maturation/remodeling phase of healing can last up to how long?
   a. 6 to 8 weeks
   b. 3 to 6 months
   c. 1 to 2 years
   d. None of the above

5. Which one of the following statements best describes common tendon injuries?
   a. The histopathology of overuse in tendons is consistent with tendonitis and is characterized by microtraumatic injury and inflammation.
   b. The histopathology of overuse in tendons is consistent with tendinosis and is characterized by microtraumatic injury and minimal inflammation.
   c. The histopathology of overuse in tendons is consistent with tendinosis and is characterized by microtraumatic injury and lack of inflammation.
   d. The histopathology of overuse in tendons is consistent with tendonitis and is characterized by microtraumatic injury and minimal inflammation.

6. The pathophysiology of delayed-onset muscle soreness (DOMS) is characterized by fibroblast activation and elevated plasma creatine kinase (CK) levels. True or false?
   a. True
   b. False

7. Which one of the following statements about rest, ice, compression, and elevation (RICE) is not true?
   a. Compression is clinically proven to improve outcome.
   b. The efficacy of RICE is generally well accepted clinically.
   c. Extended immobilization may result in tissue atrophy.
   d. Controlled muscle stretching and joint movement may improve collagen fiber orientation.

8. The results of studies investigating the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in DOMS are clear, there is a significant benefit for treating muscle soreness. True or False?
   a. True
   b. False

9. Which of the following statements about cyclooxygenase-2 (COX-2)–selective NSAIDs is/are true?
   a. The APPROVe trial did not consider a history of cardiovascular disease as part of its exclusion criteria.
   b. The VIGOR data show a 2-fold increase in the incidence of stroke.
   c. A recent cancer prevention trial showed a significant increase in the risk of cardiovascular events for the patients taking celecoxib.
   d. A meta-analysis has demonstrated that the annualized myocardial infarction (MI) rates for COX-2–selective NSAIDs in VIGOR and CLASS were significantly higher than with placebo.
   e. Both c and d

10. Which of the following statements about selective and nonselective NSAIDs is/are true?
    a. The APPROVe data demonstrated that 3.5% of rofecoxib-treated patients had MI or stroke compared with 1.9% of placebo-treated patients.
    b. Posttrial analyses of the VIGOR data show conclusively that MI rates in rofecoxib-treated patients were actually due to the cardioprotective effects of the comparator drug naproxen.
    c. Neither rofecoxib nor celecoxib have demonstrated any effect on systolic blood pressure and edema.
    d. There is evidence to suggest that COX-2–selective agents may impair renal function and cause sodium retention in patients with mild pre-existing renal failure.
    e. Both a and d

Please record your posttest answers: 1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____ Please see page 8 for the Answer Key.

REGISTRATION/EVALUATION FORM

The University of Colorado School of Medicine would appreciate your comments regarding the quality of the information presented and thanks you for your participation.

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. The program objectives were fully met.	a	b	c	d
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.	a	b	c	d
3. The educational activity has enhanced my professional effectiveness and improved my ability to:				
A. Treat/manage patients	a	b	c	d
B. Communicate with patients	a	b	c	d
C. Manage my medical practice	a	b	c	d
4. The information presented was without promotional or commercial bias.	a	b	c	d
5. The program level was appropriate.	a	b	c	d

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