An Overview Of The Physiology And Pharmacology Of Aspirin And Nonsteroidal Anti-inflammatory Drugs

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Abstract: *In this article, I present an overview of the actions and effects of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Although athletic trainers cannot prescribe or dispense prescription medications, they should be as aware of their effects as they are of other methods of injury treatment. To set the discussion in proper perspective, the inflammatory process and its mediators are reviewed briefly. The eicosanoids are a family of very active chemicals, which include: the prostaglandins, thromboxane, and the leukotrienes. They affect inflammation as well as numerous other body processes. Ingesting aspirin and NSAIDs blocks the production of prostaglandins and thromboxane, resulting in desired and undesired effects. The NSAIDs were developed to have the same action as aspirin, but with fewer adverse side effects. Many NSAIDs are currently available, and the decision as to which agent to use depends upon various factors. Surprisingly, recent studies suggest that some NSAIDs may hinder the healing process. Although not a NSAID, acetaminophen has many important clinical uses. Armed with an understanding of how these drugs act, and their potentially harmful aspects, the athletic trainer can assist the team physician in designing an aspirin- or NSAID-therapy regimen.*

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Every day, athletic trainers administer therapeutic modalities, such as electrical stimulation and ultrasound, as per the advice and guidance of the team physician. The purpose of such therapy is to bring about a rapid and complete resolution of the injury. The treatment plan is devised and agreed upon by the athletic trainer and the team physician, each drawing upon his/her education and past experiences to develop the most beneficial program. In recent years, that treatment plan has come to include prescription and over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) on a regular basis.

The use of NSAIDs and aspirin in the treatment of sports-related injuries has increased in conjunction with the growing popularity of sports and exercise.[18] In fact, there were 70.3 million NSAID prescriptions filled in the United States in 1991.[3] Past studies have shown that NSAIDs and aspirin, when included with traditional acute injury therapy, decrease pain and swelling and hasten an athlete's return to competition.[18] Chronic injury research has been less extensive, but results indicate that certain NSAIDs have positive analgesic and significant anti-inflammatory properties.[6] Recent research suggests, however, that some NSAIDs may actually slow the mechanism of tissue repair.[4,8,10,15] As a note of clarification, aspirin is technically a NSAID, but is not included in the generic term which describes the newer agents.

Obviously, athletic trainers cannot prescribe medications to injured athletes. Why, then, is this a relevant area of discussion? If the athletic trainer understands the actions, indications, and side effects of these agents, he/she can then play as large a role in NSAID-therapy decisions as in any other rehabilitation plan. An understanding of drug actions and effects also enables the athletic trainer to educate athletes about the treatment plan and the symptoms that may result from aspirin or NSAID therapy.

Legal Aspects

Laws regulating an athletic trainer's administration of various electronic modalities differ from state to state. The laws regarding our role in dispensing and administering prescription medication, though, are quite clear. Under current law, physicians cannot delegate the authority of prescribing, administering, or dispensing prescription medications to athletic trainers.[24] Laws governing dispensing OTC medications also vary by state.[38] I recommend that athletic trainers currently involved in the dispensing of either prescription or OTC medications immediately become familiar with, and conform to, state laws and/or the guidelines of their governing body (NCAA, NAIA, National High School Federation, etc) or school district (See Whitehill, etal[38]).

The Inflammatory Response

To set our discussion in proper perspective, a brief review of the inflammatory response is necessary. Inflammation is the response of vascular tissue to physiological damage. The response prevents the extensive spread of injury-causing agents to nearby tissues, disposes of cellular debris, and sets the stage for the repair process.[21] The process begins with the initial tissue trauma. Following a short period of vasoconstriction, the cellular injury signals the release of chemical mediators, such as histamine, bradykinin, thromboxane, leukotrienes, and prosta-

glandins.[34] These chemical mediators increase cellular and capillary permeability and stimulate capillary vasodilation. The changes in vascular permeability directly result in edema, due to the flow of fluid into the interstitial space.[32] The increased blood flow and permeability allow for white blood cells to migrate toward the injury site, infiltrate the site, and initiate the healing process.[5] Within 48 hours of the initial insult, fibroblasts begin the process of wound repair and collagen synthesis.[32]

The inflammatory response is essential to the resolution of the injury. However, excessive edema, coupled with vascular damage, can disrupt the flow of oxygen to the healthy tissue surrounding the injury site. The resultant hypoxia can lead to further tissue damage, appropriately referred to as secondary hypoxic injury.[17]

The use of cryotherapy and other modalities in an effort to decrease pain and inflammation have been understood by sports medicine professionals for several years.[17] The following discussion will shed light upon the specific roles played by various chemical mediators in the inflammatory response and how physician-prescribed and -administered pharmaceuticals affect that process.

The Eicosanoid Family

As noted earlier, the prostaglandins, thromboxane, and the leukotrienes all play a role in the inflammatory response. They are all members of the eicosanoid family, derivatives of the 20-carbon fatty acid molecule arachidonic acid (Fig 1). Arachidonic acid is a component of cell membranes and must be released from the membrane prior to its being synthesized to an eicosanoid. Once free, arachidonic acid can be converted to either an initial leukotriene or to a common prostaglandin and thromboxane precursor via two separate pathways. Aspirin and NSAIDs exert their effects by blocking the production of prostaglandins and thromboxanes. Most of these agents have little or no effect upon leukotriene synthesis.

Leukotrienes

Leukotrienes are synthesized from arachidonic acid by the action of the enzyme lipoxygenase. The leukotrienes consist of a family of chemicals which function to mediate chemotaxis, increase vascular permeability, and activate leukocytes.[12] Most pharmacologic agents which block leukotriene production have been too unspecific or toxic so far to use therapeutically.[12]

Prostaglandins and Thromboxane

The prostaglandins represent a variety of very important chemicals that are produced by almost every tissue of the body. Different prostaglandins play various roles in many physiological processes. Those roles are examined in the following discussion and outlined in Table 1.

Mediation of Inflammatory Process. The term mediation is important in describing the activities of prostaglandins. On their own, prostaglandins do not appear to be capable of inducing either pain or edema.[13] They are capable, however, of directly causing vasodilation, but are dependent upon histamine and bradykinin to increase the permeability of the blood vessels. In addition, prostaglandins act synergistically with other chemicals to sensitize pain receptors to mechanical and chemical stimulation.[23]

Fever Mediation. Prostaglandins have been implicated in the role of fever mediation through their release into the hypothalamus. The hypothalamus acts

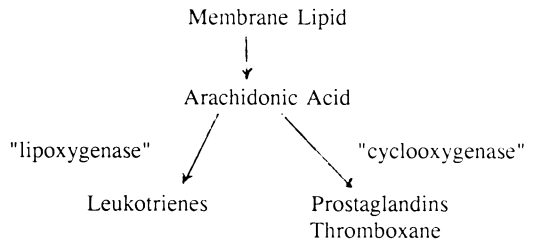

Fig 1.—The stepwise synthesis of the eicosanoid family. Quotation marks denote the enzymes involved in the pathway.

Table 1.— A Summary of the Major Effects of the Eicosanoids

Eicosanoids	Major Effects
Leukotrienes	Chemotaxis
	Leukocyte activation
	Increase in vascular permeability
Thromboxane	Platelet aggregation
Prostaglandins	Mediation of inflammation
	Increase in vascular permeability*
	Sensitization of pain receptors*
	Mediation of fever
	Induction of uterine contractions
	Inhibition of gastric secretion
	"Cytoprotection" of gastric mucosa
	Systemic and renal vasodilation
	Inhibition of platelet aggregation

Note: asterisk denotes synergistic actions.

as the thermoregulatory control center of the body. Although the exact mechanism remains unknown, injection of specific prostaglandins into the cerebral ventricles of animals causes an increase in body temperature.[33]

Gastric Protection. Prostaglandins interact in a number of ways to protect the delicate lining of the gastrointestinal system. They appear to inhibit gastric acid secretion and may have an anti-ulcer effect.[31] Prostaglandins also appear to have the property of "cytoprotection," the ability to protect the gastric mucosa from exposure to harmful substances. Though the mechanism is unknown, cytoprotection may result from a specific prostaglandin which stimulates mucous formation.[31]

Reproductive System. In the uterus, prostaglandins act to stimulate the contraction of the smooth muscle layer, known as the myometrium. This smooth muscle contraction serves two important purposes. During childbirth, the prostaglandin-stimulated contractions of the myometrium aid in delivering the baby through the birth canal. They are also released at the end of the menstrual cycle to facilitate the shedding of the uterine lining by stimulating muscular contractions.[14] These continuous contractions can result in ischemic pain, referred to as "cramping" or primary dysmenorrhea.

Renal Blood Flow. During exercise, the autonomic nervous system releases into the bloodstream chemicals which act as potent vasoconstrictors in many peripheral tissues, including the kidneys. Prostaglandins can serve to dilate renal blood vessels, counteracting those chemicals, thus maintaining a constant flow of blood to the kidneys.[26] This action of the prostaglandins appears to be more significant if the kidneys are functioning abnormally.[16]

Other Effects. A specific prostaglandin, prostacyclin, is released by the internal lining of the blood vessels. This substance appears to inhibit the aggregation of blood platelets on blood vessel walls. Also highlighting the importance of prostaglandins, a recent study suggests that they may promote the repair of cartilage by inhibiting the action of interleukin-1.[9] This discovery could be of major importance for people suffering from rheumatoid arthritis.

Thromboxane

Thromboxane, produced in blood platelets, functions as a powerful inducer of blood platelet aggregation to aide in the clotting mechanism.[12] Therefore, thromboxane and prostacyclin have an antagonistic relationship. This stands as a good example of how prostaglandins are used naturally to attenuate the actions of other chemicals in a variety of tissues.

This basic discussion of the inflammatory response and the properties of the arachidonic acid derivatives sets the stage for discussing how aspirin and the different NSAIDs can affect these processes.

Aspirin

Aspirin (acetylsalicylic acid) is a derivative of salicylic acid. Found in the bark of willow trees, salicylic acid's medicinal benefits and side effects have been known for more than 2000 years. Aspirin was first synthesized by a Bayer Company chemist in the late 19th century. It proved to be far less of a gastric irritant than salicylic acid and was introduced to the marketplace in the spring of 1899. Heralded as a wonder drug, it quickly became one of the most widely used pharmaceutical products in the world. Annual aspirin consumption in the United States now ranges between 26 and 74 million pounds.[23]

Surprisingly, aspirin's mechanism of action has been known only since 1971. John Vane discovered that the aspirin molecule transfers a functional group onto the cyclooxygenase enzyme.[35] As a result, the enzyme is irreversibly inhibited and unable to bind arachidonic acid; therefore, the enzyme can no longer convert arachidonic acid to prostaglandins and thromboxane.

Effects of Aspirin

Following the ingestion of aspirin (3000 to 6000 mg per day for anti-inflammatory action), a series of chemical events results from the blockage of cyclooxygenase. The decrease in prostaglandin production leads to a corresponding reduction in inflammation and edema.[16] The inhibition of prostaglandin and thromboxane synthesis may not be the only effect that aspirin exerts upon the tissues. In some systems, aspirin might impinge upon the formation of 12-HETE, a leukotriene derivative that acts as a chemotactic agent.[16] Aspirin might also reduce inflammation and pain by influencing the migration of chemical potentiators, such as neutrophils and monocytes, and activate neutrophils as well.[16]

Negative consequences might also result from aspirin use. In the gastrointestinal tract, aspirin can cause gastric upset, bleeding, and even ulcers. Various studies have shown an incidence of anywhere from 2% to 40%, depending upon the parameters of the investigation.[16] It does not appear that the gastrointestinal side effects are due to inhibiting prostaglandin synthesis alone, although this area is controversial.[16,28]

The mechanism of gastric irritation does, however, appear to be related to the direct effect of aspirin upon the lining of the stomach.[19] Unbuffered aspirin lowers the electrical potential of the gastric membrane, which then affects the flow of hydrogen ions. Davenport's theory contends that this disruption of hydrogen ions triggers a series of events which lead to gastric erosion and bleeding.[16] Studies have shown that enteric-coated aspirin does not cause as many abnormalities in the stomach lining, due to its buffering action.[16] Mild gastrointestinal upset often can be avoided if aspirin is taken with a meal, due to the "buffering" action of the food.

Aspirin use can also result in complications such as prolonged bleeding time and tinnitus. Prolonged bleeding time results from the inhibition of thromboxane. Since aspirin irreversibly binds to cyclooxygenase, the decreased platelet function lasts from 4 to 6 days (the platelet lifespan) following aspirin intake.[28] In addition, many people taking high doses of aspirin develop a ringing in their ears (tinnitus). It probably is due to an effect upon the inner ear, rather than the central nervous system, and often results from a dosage that is too high.

Reye's Syndrome

First described in 1963, Reye's syndrome is a rare and potentially devastating acute illness that usually strikes children following a viral infection. For several years, epidemiological data suggested a relationship between Reye's syndrome and aspirin use by children infected with either the influenza or chicken pox virus. Those early reports were criticized highly. More recently, a study conducted by the Centers for Disease Control linked aspirin and other salicylates to the occurrence of Reye's syndrome when administered in the management of viral illnesses.[7] Based upon current knowledge, it would appear prudent to not allow anyone under the age of 18, who may have a viral infection, to use aspirin and other salicylates.

Although the cause of Reye's syndrome is unknown, it is known that the illness impairs mitochondrial function, resulting in liver and neurological damage.[37] In 1974, Lovejoy et al[20] proposed a five-stage system on which to chart the symptoms of Reye's syndrome (Table 2).

Reye's syndrome is a potentially fatal condition, and the symptoms must be treated as a medical emergency. However, a diagnosis can be made only through various laboratory tests.

The NSAIDS

In the latter half of this century, chemists have used aspirin as a prototype to develop the group of drugs known as NSAIDs. The main goal of this research is to produce agents that do not present aspirin's sometimes severe side effects. Although there are differences in potency, specificity, and specific mechanisms of action, all NSAIDs inhibit the activity of cyclooxygenase in some manner.[13] The inhibition is not an irreversible reaction like aspirin, but instead, dependent upon concentration.[28]

Along with blocking cyclo- oxygenase, NSAIDs are thought to have additional properties. Possible activities include modulation of T-cell function, inhibition of inflammatory cell chemotaxis, lysosomal membrane stabilization, and free radical scavenging.[2,28] The beneficial activities of the different NSAIDs seem to be quite similar, although there are some differences in action and side effects.

Many different chemical classes and brands of NSAIDs are currently available. New NSAIDs are introduced to the market monthly. The following discussion represents a clinical overview of frequently used chemical classes of NSAIDs (Table 3), as well as those agents with special clinical significance and their standard prescription dosages. The doses listed are for anti-inflammatory action unless otherwise noted. Analgesic doses tend to be 50% to 75% of inflammation-fighting doses.

Ibuprofen (Advil, Motrin, Nuprin)

A propionic acid derivative, ibuprofen is the most frequently prescribed NSAID.[3] It boasts aspirin's potency for analgesic and anti-inflammatory action, but has a lower incidence of side effects. This reduced incidence may be linked to ibuprofen's decreased inhibition of platelet aggregation, lessening possible gastric bleeding.[33] In addition, it appears that ibuprofen may be the most beneficial NSAID for easing the pain of primary dysmenorrhea. A prescription regimen consists of 2200 to 2400 mg per day, taken in three separate doses.[7,22,25] Such a schedule enables it to be taken at meal times, lessening the likelihood of gastric irritation, as mentioned above, and may improve compliance. Daily dosage should not exceed 3200 mg.[2]

Naproxen (Naprosyn)

The second most-prescribed NSAID, naproxen is chemically similar to ibuprofen.[3] Naproxen is 20% more potent than aspirin, with side effects much like ibuprofen.[33] In comparison to ibuprofen, naproxen was marginally superior in decreasing joint inflammation.[25] Due to naproxen's long half-life, the daily recommended dosage of 750 to 1000 mg can be taken on a twice daily schedule, reducing gastric upset due to only two daily exposures.[2,7] Naproxen is eliminated from the body mainly by way of the kidneys; therefore, it should be used with caution in persons with renal complications.[2]

Fenoprofen (Nalfon)

This agent deserves special mention because it appears to be more damaging to the kidneys than other NSAIDs of the propionic class.[28] The reason for this apparent relationship is unknown. However, in a study of people suffering from rheumatoid arthritis, fenoprofen was

Table 2.— Stages of Reye's Syndrome

Stage	Signs and Symptoms
1	Vomiting, Lethargy, Indifference
2	Delirium, Hyperventilation, Combativeness
3	Light coma, Hypoventilation, Intact pupillary response, Decorticate posturing
4	Deep coma, Loss of spontaneous ventilation, Decerebrate posturing, Fixed and dilated pupils
5	Flacidity, Seizures

Adapted from Lovejoy, et al.[20]

Table 3.— Chemical Classes of NSAIDs

Carboxylic Acids			Enolic Acids		
Propionic	Acetic	Salicylic	Oxicams	Pyrazolones	Pyrrolopyrrole
Naproxen	Indomethacin	Aspirin	Piroxicam	Phenylbutazone	Ketorolac
Ibuprofen	Tolmetin				
Fenoprofen	Diclofenac				

Table 4.— Cost of NSAID Therapy

Drug	Usual Dosage	Cost
Diclofenac sodium-*Voltaren* (Geigy)	50mg tid or 75mg qid	$36.07
Fenoprofen-*Nalfon* (Dista)	300-600mg tid or qid	$31.45
Ibuprofen-*Motrin* (Upjohn)	600-800mg tid or qid	$15.50
Indomethacin-*Indocin* (MSD)	25mg tid or qid	$20.36
Indocin-RS (MSD)	75mg once or bid	$18.90
Naproxen-*Naprosyn* (Syntex)	375-500mg bid	$25.75
Piroxicam-*Feldene* (Pfizer)	20mg once per day	$37.41
Tolmetin-*Tolectin* (McNeil)	200-400mg tid or qid	$32.72

Cost of treatment is the pharmacist's wholesale cost for a 14-day treatment at the lowest usual dosage for anti-inflammatory effect. Prices from 1993 *Redbook*.[30]

Table 5.— Drugs Which May Interact With NSAIDs and Their Common Clinical Uses

Drug	Common Use
Angiotensin-converting enzyme (ACE) inhibitor (Capoten, others)	Treatment of hypertension
Anticoagulants (Coumadin, Panwarfin)	Prophylaxis and treatment of pulmonary embolism and venous thrombosis
Beta Blockers (Inderal, others)	Decrease cardiac output and peripheral vascular resistance
Diuretics (Lasix, others)	Promote the excretion of urine
Lithium	Treatment of manic depression
Methotrexate	Treatment of cancer
Metoclopramide (Reglan)	Anti-emetic
Phenytoin Sodium (Dilantin)	Treatment of seizure disorders
Probenecid (Benemid)	Treatment of gout, maintenance of serum levels of cephalosporins or penicillins
Sulfonylureas (Glucotrol, others)	Treatment of noninsulin-dependent diabetes

found to have fewer gastrointestinal side effects than the other NSAIDs to which it was compared.[28] Usual dosage consists of 300 to 600 mg, three or four times daily, with total dosage not exceeding 3200 mg.[2] Due to the increased incidence of renal damage, fenoprofen should be used cautiously.

Piroxicam (Feldene)

Although derived from a different chemical group, piroxicam has properties similar to ibuprofen, naproxen, and fenoprofen. Piroxicam's most important asset lies in its once-a-day dosage schedule of 20 mg.[2,7] The single daily dose greatly benefits compliance, and gastrointestinal irritation can be decreased even more if the drug is taken with the largest meal of the day.[6] Piroxicam has been found to increase the percentage of suppressor T cells in peripheral blood and to inhibit neutrophil migration.[2,28] Such research suggests that a person with a cold or other infection should avoid the drug. Piroxicam is cleared from the plasma mainly by the liver; hence, it can be administered to people with renal deficiency.[28]

Tolmetin (Tolectin)

Tolectin is chemically different than the previously discussed NSAIDs, but has similar effects. The most frequently reported side effect is gastrointestinal disturbance.[2] When given in conjunction with acetaminophen, the analgesic properties of tolmetin are enhanced.[2] Tolmetin is administered in three or four doses of 200 to 400 mg. A daily dose of 1200 to 1500 mg roughly approximates 2400 mg of ibuprofen.[28]

Diclofenac Sodium (Voltaren)

As with other NSAIDs, diclofenac inhibits the synthesis of prostaglandins and thromboxane. However, it also reduces the amount of arachidonic acid made available from the cell membrane, thereby decreasing the amount of leukotrienes produced as well.[2] Standard dosage is 50 mg three times per day or 75 mg twice a day.[2] In addition, renal damage may be associated with diclofenac less frequently, but this is yet to be verified.[2]

Indomethacin (Indocin)

Indomethacin, introduced in 1963, was one of the first NSAIDs developed and continues to be among the most powerful inhibitors of cyclo-oxygenase.[18] Although particularly effective in maladies such as rheumatoid arthritis, ankylosing spondylitis, and gout arthritis, indomethacin is not recommended for use as a simple analgesic or antipyretic due to potentially severe side effects such as gastrointestinal disturbances and headaches.[2] Daily dosage ranges from 75 to 100 mg taken in three or four doses.[2] Prolonged release formulas are available (75 mg one to two times per day); however, gastrointesinal and other adverse effects appear to be similar to those associated with the regular formula.[2]

Ketorolac Tromethamine (Toradol)

Recently introduced, ketorolac is the first NSAID to be available for intramuscular injection, as well as oral administration. Although it also has anti-inflammatory and antipyretic properties, it currently is being marketed only as an analgesic, particularly for postoperative patients.[2] Studies have shown ketorolac to be equal to, or more effective than, morphine.[27,39] Although administered intramuscularly, damage to the gastrointestinal mucosa still occurs. However, doses of 10 to 30 mg given 4 to 5 times per day produced less mucosal injury than 650 mg of aspirin using the same dosage schedule.[2] The

maximum recommended daily dose is 150 mg for the first day, followed by no more than 120 mg per day for the remainder of the regimen.[2] Ketorolac represents an exciting step in NSAID development, an agent with the analgesic efficacy of morphine, easily delivered, and nonaddictive.

Phenylbutazone (Butazolidin)

Introduced in 1949, phenylbutazone has decreased in popularity with the development of less toxic NSAIDs. Its use is recommended only after other NSAID therapies have failed, and then only if the physician and patient decide that the benefits outweigh the risks of therapy.[2] The long-term use of phenylbutazone can result in various blood dyscrasias, including aplastic anemia (destruction of red bone marrow) and severe hepatic reactions.[28] At the present time, phenylbutazone's significance is more historical than clinical.

Choosing an NSAID

The main considerations in the design of an NSAID- or aspirin-therapy regimen are efficacy of the agent, patient compliance, adverse side effects, and cost of treatment. Incidence and severity of side effects weigh heavily upon compliance and treatment cost. Compliance is attained more easily if the drug causes minimal discomfort and the dosage requirements easily fit into the patient's schedule. The cost of treatment can be a difficult figure to attain because there are other factors besides the cost of the drugs which are listed in Table 4. An inexpensive option, such as aspirin, can become quite expensive if an ulcer or other gastrointestinal pathology develops and requires more medication or even hospitalization.[6]

An additional factor to consider in designing an NSAID program has recently been discovered. Several studies have shown that NSAIDs may have the ability to slow the healing process. In a study conducted by culturing rabbit articular cartilage chondrocytes in the presence of certain NSAIDs, diclofenac and indomethacin (and piroxicam to a lesser degree) inhibited the secretion of proteoglycans.[8] Proteoglycans are extracellular molecules involved in the formation of cartilage, tendons, and ligaments. They are vital to the process of tissue repair. Other studies have shown that indomethacin and aspirin can interfere with the synthesis or transport of such connective tissue components.[4,10,15]

In contrast to the findings above, a recent study indicated that indomethacin, diclofenac, and piroxicam are capable of suppressing enzymes responsible for the degradation of collagen and cartilage.[36] Such results indicate that NSAIDs may diminish the process of osteoarthritis. These areas of NSAID activity are certain to be the focus of intensive investigation and controversy for the next several years.

Controversy also exists over when an NSAID regimen should begin following an acute injury. Some feel drug therapy should be initiated immediately along with rest, ice, compression, and elevation (RICE) in an attempt to arrest the inflammatory process. Others believe that NSAID therapy should begin no sooner than 24 hours following the injury and implementation of RICE, the idea being that the NSAIDs blockage of thromboxane synthesis will promote additional bleeding. Evidence on either side of the argument is largely anecdotal, most coming from the clinical setting. Very little research exists in this area.

Drug Interactions

NSAIDs bind strongly to plasma proteins, thus competing for binding sites with other agents. Usually, such interactions are of little clinical significance, except when NSAIDs are used in conjunction with other highly bound drugs (Table 5). Therefore, caution should be taken before combining NSAID therapy with drugs such as methotrexate, phenytoin sodium (Dilantin), warfarin sodium (Coumadin, Panwarfin), captopril (Capoten), and ionically bound oral hypoglycemics.[1] Concomitant use of NSAIDs and lithium has resulted in lithium toxicity due to a decrease in the renal clearance of lithium.[1] Owing to the variability of possible reactions and the large number of potential reactive agents, I recommend that the athletic trainer keep a list of ALL medications each athlete is taking so that the information can be readily available to the physician and athletic trainer when designing a NSAID-therapy regimen.

Acetaminophen

Although not an anti-inflammatory agent, acetaminophen (Tylenol, Anacin 3) is an important drug and deserves our attention, due to its clinical uses. Acetaminophen, discovered in 1877, has analgesic and antipyretic properties through its actions upon the central nervous system. Acetaminophen has no anti-inflammatory properties because it cannot inhibit cyclooxygenase in the peripheral tissues.[29] So, it does not present complications such as gastrointestinal disturbance and prolonged bleeding time. Therefore, acetaminophen is indicated for mild pain and fever in those who are either contraindicated for aspirin use due to Reye's syndrome risk (see above) or those who cannot tolerate aspirin or NSAIDs. Usual dosage of acetaminophen is 325 to 650 mg at 4-hour intervals.[2]

Acetaminophen, like all drugs, can be a toxic substance if abused. The minimum toxic dose in adults is 5 to 15 g.[11] Overdoses or prolonged overuse (5 to 8g per day for several days) might result in severe hepatic damage or death.[2] The liver damage appears to be produced by a metabolite of acetaminophen. In therapeutic doses, the toxic metabolite is detoxified by glutathione; however, with extreme intake, if the glutathione drops below 30% of normal values, tissue necrosis occurs.[11]

Conclusion

Aspirin and NSAIDs currently play an important role in the treatment of musculoskeletal injuries and other disease processes. In many instances, they can be as important in the rehabilitation program as the traditional modalities which all athletic trainers apply and understand. The fact that we cannot prescribe or dispense these medications should not discourage interest in the subject.

The field of NSAID pharmacology is constantly changing, making it difficult to follow every new development and

study. The knowledgeable and informed athletic trainer can be a valuable ally to the team physician by following NSAID developments. Additionally, the athletic trainer is in the best position to monitor compliance and the occurrence of side effects. This type of working relationship with a physician can only serve to improve the level of care given to athletes and patients.

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