CHAPTER **43**

RISK CONSIDERATIONS FOR THE USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed class of medications by podiatrists and orthopedists. However, a number of questions may arise when we prescribe these to our patients. We are all aware that NSAIDs can cause serious side effects, but determining how to implement proper therapy in light of the potential complications is often challenging. Also, from a patient education standpoint, what information should we make clear to the patient regarding the use of NSAIDs?

MECHANISM OF ACTION OF NSAIDS

When cells are injured, cyclooxygenase (COX) transforms phospholipid-derived arachidonic acid into prostaglandins, which in turn, cause inflammation. NSAIDs reduce that inflammation by interrupting the cyclooxygenase cascade. NSAIDs interrupt the synthesis of prostaglandins, which are subsequently unable to sensitize nociceptors to mechanical or chemical stimuli. This raises the stimulatory threshold of C-fiber polymodal nociceptors.

The COX enzyme exists in 2 isoforms, COX-1 and COX-2. The COX-1 isoenzymes produce prostaglandins that are present in and help protect the gastrointestinal (GI) tract. These prostaglandins act by helping to maintain normal gastric and duodenal mucosa integrity. The COX-2 isoenzymes produce prostaglandins that mediate an immune response and come into play to help damaged mucosa heal. Therefore, blocking prostaglandins, while helping reduce inflammation in one body part, is not a good thing for the GI tract. Traditional nonselective NSAIDs, which are derived from carboxylic and enolic acids, inhibit both the COX-1 and COX-2 isoenzymes. Primarily due to the COX-1 inhibition, traditional nonselective NSAIDs can more often lead to serious GI side effects. It was these side effects that led to the development of coxibs, which are a group of NSAIDs that selectively inhibit the COX-2 isoenzyme. An example is Celebrex (celecoxib). The coxibs reduce but do not eliminate the GI side effects attributed to traditional NSAIDs.

GI SIDE EFFECTS

Currently, 60% of all NSAID users experience side GI side effects. These side effects range from minor dyspepsia (stomach upset) to severe perforated ulcerations. Endoscopic studies have indicated that 20-30% of traditional NSAID users develop GI ulcers. COX-2 inhibitors decrease but do not eliminate the rate of severe GI complications. Researchers have shown that the risk of serious GI complications decreases by 50-60% when patients use COX-2 inhibitors in comparison with traditional NSAIDs. Thus, the likelihood of development of a GI ulcer when taking a selective NSAID would drop to less than 1%.

The GI literature states that 100,000 hospitalizations and 10,000 deaths occur each year due to the use of NSAIDs. In a relatively recent study, 20% of NSAID users had endoscopic evidence of an ulceration; however only 10% of that 20% had symptoms or complications. Therefore, only about 2% of those patients chronically taking NSAID's have symptoms (bleeding, perforation, or obstruction). Interestingly enough, deep NSAID ulcers frequently present without pain unless they perforate. The patients with dyspepsia caused by NSAIDs usually are found to have only a superficial gastritis. This is probably a contact (pill to mucosa) problem and resolves rapidly after discontinuing the drug. The deep ulcerations are due to the systemic effect of the drugs. That is how intramuscular NSAIDs (such as Toradol) can cause ulcerations.

Furthermore, COX-1, (which is present in platelets) when inhibited, increases bleeding tendencies. Therefore, NSAID ulcers tend to bleed more than ulcers from other causes such as Helicobacter pylori. In general, the GI complications of NSAIDs occur in daily users taken over several weeks to years. Gastroenterologists report that they have seen ulcers after only 2 weeks of heavy use. Higher doses of any of the NSAIDs are more likely to cause ulcers. Some NSAIDs are more ulcerogenic than others. As an example, Indocin and Voltaren are on the high risk end of the scale whereas Mobic and Relafen are generally considered to be safer. Adding aspirin or a second NSAID also increases the risk of ulceration. In fact, adding aspirin to a patient taking a COX-2 erases the protection that it is

meant to provide, and the ulcer rate is the same as if they were taking a nonselective NSAID. The amount of aspirin can be as little as the 81mg recommended by a cardiologist.

One should take into consideration which patients are more likely to develop ulcers from NSAIDs. The following are considered risk factors:

1. Personal history of peptic ulcer disease
2. Concurrent use of more than one NSAID
3. Use of a higher dose of the NSAID
4. Concurrent use of anticoagulant (warfarin or platelet inhibitors)
5. Age >60 years
6. Concurrent use of corticosteroids

A fair amount of research has been conducted to study the use of other medications to provide some protection while a patient is taking NSAIDS. Originally, H2 receptor antagonists (such as cimetidine, ranitidine, and Pepcid) were evaluated. However, it was learned that these medications do not prevent ulcers in patients on NSAIDs. They do help the dyspepsia caused by the superficial gastritis. An older drug, Cytotec, does offer protection from ulcers but it has to be taken 4 times daily, and has potential complications of diarrhea and induction of miscarriages. It has largely been replaced by the proton pump inhibitors (PPI) such as Prilosec (omprazole), Nexium, Zegerid, and Protonix (now generic pantoprazole), Prevacid and Aciphex. All of these offer some degree of protection. There is some concern whether Pirolsec OTC, which is only 20 mg, offers enough protection, therefore if a PPI is going to be used, a prescription strength medication should probably be used.

It has also been well established that NSAIDs can cause ulcerations in the small intestine as well as the colon. The good news is, like stomach ulcers, the majority do not cause symptoms. Unfortunately, there are no protective drugs for distal GI ulcers.

INTERSTITIAL NEPHRITIS

Interstitial nephritis is a kidney disorder in which the spaces between the kidney tubules become swollen and inflamed. The inflammation can affect the kidneys' ability to filter waste and can be a very serious condition. NSAIDs are a known risk factor that can lead to this condition. Interstitial nephritis is more common in elderly people, perhaps because of the higher incidence of arthritic disorders in this population. It is essentially a hypersensitivity reaction. Acute allergic interstitial nephritis should not be confused with the acute vasomotor renal insufficiency that can occur in patients with preexisting underperfusion of the kidney. A unique feature of allergic interstitial nephritis caused by NSAIDs is that patients may present with nephrotic syndrome. In such patients, massive proteinuria with hypoalbuminemia and edema are present in addition to the typical features of acute interstitial nephritis. Findings on kidney biopsy show features of minimal change nephrosis in addition to the characteristic findings of interstitial nephritis.

NSAIDs can cause acute interstitial nephritis, which many times is reversible. Patients with acute tubulointerstitial nephritis caused by NSAIDs typically present with heavy proteinuria, often in the nephrotic range. Cessation of the offending agent usually, but not always, results in complete recovery. However, the rate of recovery is variable, and, in some patients, renal failure persists for many weeks before renal function improves. Physical examination may provide clues to the diagnosis (e.g., fever, rash in acute tubulointerstitial nephritis, livido reticularis), but in most patients, no characteristic findings exist.

ANALGESIC NEPHROPATHY

Analgesic nephropathy is the most common category of chronic interstitial nephritis worldwide. This disorder occurs with long-term ingestion of combinations of phenacetin, aspirin, and caffeine or phenacetin-acetaminophen or NSAIDs and acetaminophen. In its most severe form, it is associated with papillary necrosis. The amount of phenacetin-acetaminophen combination required to cause chronic interstitial nephritis has been estimated to be at least 2-3 kg over many years. Although initially thought to be exclusively associated with phenacetin-containing combinations, all analgesics, including acetaminophen, aspirin, and NSAIDs, can cause analgesic-induced chronic tubulointerstitial nephritis.

Analgesic nephropathy is most common in women in the sixth and seventh decades of life who have a history of low back pain, migraine headaches, or other chronic musculoskeletal pain. In some patients, a history can be elicited of episodes of papillary necrosis, i.e., gross hematuria with flank pain occasionally accompanied by obstruction and infection. Clinically, patients with analgesic nephropathy present with renal insufficiency, modest proteinuria, sterile pyuria, and anemia. Diagnosis can be supported by history of heavy analgesic use, and computer-assisted tomograms may reveal microcalcifications at the papillary tips.

RISK OF CAUSING CARDIOVASCULAR DISEASE

The use of COX-2 inhibitors has been connected with an increased risk of cardiovascular events and death. Haag found a greater risk of stroke with the use of NSAIDs in

the general population. The risk of stroke was most pronounced with COX-2 selective NSAID use. In addition, The Alzheimer Disease Anti-Inflammatory Prevention Trial (ADAPT) has shown that patients taking naproxen were twice as likely to suffer a stroke compared to the placebo group. During another study, there was a 2-fold increase in patients with a cerebrovascular events in comparison with a placebo group after 36 months.

In another study it was shown that patients on rofecoxib who were also being treated for hypertension had double the risk of thromboembolic cardiovascular events in comparison with those taking celecoxib, traditional NSAIDs, or patients not taking any NSAID at all.

The APPROVE trial reported an increased risk of myocardial infarction and stroke in patients taking rofecoxib and this study later led to the withdrawal of the drug in 2004. Valdecoxib was withdrawn from the market in 2005 following 2 short-term studies of the drug in patients undergoing coronary bypass surgery who had a 4-fold greater increase in cardiovascular and thromboembolic events.

DELAYED BONE HEALING

There are some other perioperative uses of NSAIDs that deserve some consideration. One such risk is delayed bone healing, which can affect the healing of osteotomies or fractures. The prostaglandin production that NSAIDs block is thought to affect bone metabolism. Prostaglandins have significant effects on osteoclastic and osteoblastic activity, which is essential for bone repair and remodeling. Alterations in prostaglandin production have been correlated with changes in the amount of trabecular regeneration and the rate of bone healing. Prostaglandin E2 is the most potent prostaglandin that stimulates bone resorption and formation. It does this by adding bone-to-bone envelopes and inducing woven bone formation. There are a number of studies that have evaluated the effect of NSAIDs on bone healing but the results were variable. Studies have shown that rabbits and rats treated with aspirin, diclofenac, ibuprofen, indomethacin and tenoxicam have experienced impaired bone healing.

These changes in bone healing include inhibition of Haversian remodeling, poor mineralization of bone matrix, a decrease in osteoid formation, decreased bone mineral content, reduction of mechanical strength of replacement tissue, decreased amounts of cortical bone, and inhibition of new bone growth. The use of oral diclofenac lead to an increased incidence of delayed fracture healing in one murine study. However, other studies have shown that NSAIDs had no effect upon collagen synthesis in vitro in the treatment of fracture callus in rats.

The effect of NSAIDs on bone healing is not well understood. Mehallo does not recommend the use of NSAIDs in the treatment of complete fractures, stress fractures at high risk of nonunion or in patients with a chronic muscle injury. Until definitive data suggests that low-dose NSAIDs are detrimental to bone healing, if needed it is best to use the lowest effective dose of the NSAID for the shortest duration of time.

LABORATORY STUDIES

For patients who take NSAIDs long-term (such as a patient with rheumatoid arthritis), lab study monitoring is in order. Typically, the labs are performed every 6 months.

Complete blood cell count with differential

Decreased hemoglobin, hematocrit, and RBC counts can be seen with GI bleeds. Eosinophilia is sometimes seen in AIN. (However, this is neither specific nor sensitive enough to establish the diagnosis.) Although the true incidence of eosinophilia in acute tubulointerstitial nephritis is unknown, it is estimated to be present in approximately half of patients. Most typically, eosinophilia is absent in AIN-induced by NSAIDs.

Blood chemistry (complete metabolic profile)

A complete set of chemistries, including BUN and serum creatinine, provides information on whether renal insufficiency exists. A low bicarbonate level (total carbon dioxide <24-23 mEq/L) may indicate acidosis. Low serum potassium levels may indicate a proximal tubular disorder, and elevated serum potassium levels with a low bicarbonate level may indicate type 4 renal tubular acidosis, which can be observed with lead nephropathy and NSAID-induced analgesic nephropathy, among other conditions.

Urinalysis

Urinalysis may reveal proteinuria, hematuria, and the presence of white cells, with or without bacteria. A microscopic analysis of urine sediment may reveal casts, white cells, eosinophils, and crystals. If allergic interstitial nephritis is suspected, send a cytospin specimen to determine if eosinophils are in the urine. In NSAID-induced AIN, eosinophiluria is usually absent.

SUMMARY

We all prescribe NSAIDs frequently, and therefore must be aware of the potential side effects that may occur due to their use. It is important that we educate the patient regarding typically infrequent, but sometimes serious side effects. If a patient is to stay on an NSAID therapy long-term it is advised to involve the patient's primary care physician. The patient needs to fully understand the risks and benefits of use of these medications.