CHAPTER **41**

RISKS OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

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INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are routinely used in podiatric medicine and surgery. Aspirin was the first NSAID developed in the late 19th century. The more traditional NSAIDs have been developed since the mid-20th century. Aspirin and traditional NSAIDs inhibit the activity of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 inhibition leads to blockage of production of thromboxanes. COX-2 inhibition leads to blockage of synthesis of prostaglandins. Aspirin is the only NSAID to irreversibly inhibit COX-1, thereby inhibiting platelet aggregation. It is this reason that aspirin is indicated in the management of arterial thrombosis and prevention of adverse cardiovascular events. Traditional NSAIDs reversibly inhibit COX-1 and therefore do not have the same cardiovascular indications. It is the inhibition of COX-2 that leads these drugs to act as analgesics, antipyretics, and agents to reduce inflammation. Unfortunately, the inhibition of COX-1, be it reversible or irreversible, produces the risks of gastrointestinal (GI) bleeding and ulcers.

Due to the known potential GI risks and the thought that the inhibition of COX-1 and not COX-2 produced these risks, COX-2 selective inhibitors were developed in the late 20th century. The idea of development of these newer selective agents would be to maintain the anti-inflammatory and other useful properties, but reduce the GI risks and adverse events. Another advantage to the COX-2 selective NSAIDs is that without the effect on thromboxane, they have little effect on platelet aggregation.

NSAIDs are indicated for rheumatoid arthritis, osteoarthritis, inflammatory arthropathies, acute gout, dysmenorrheal, metastatic bone pain, headaches including migraines, postoperative pain, pain secondary to inflammation or tissue injury, pyrexia, and ileus. NSAIDs should be used with caution in patients with the following risk factors: decreased renal function; decreased hepatic function; history of GI ulcers, bleeds, or gastritis; low platelet count; Crohn's disease or ulcerative colitis; asthma or chronic lung disease; GERD or hiatal hernia; hypertension (HTN); congestive heart failure; past cerebrovascular accident; past myocardial infarct (MI); allergy to aspirin, sulfa drugs, or has nasal polyps; currently taking warfarin or other blood thinners; currently taking corticosteroids; pregnant; age greater than 65 years; or consumes more than 7 alcoholic beverages per week.

RISKS OF NSAIDS

Historically, prescribers were well aware of the renal and GI risk of NSAIDs. These drugs were used with caution, if at all, in patients with renal disease or past history of GI ulceration/bleed. In fact, 10 to 20% of patients taking NSAIDs will experience dyspepsia, even without a GI disease history. It is the more recently understood, and potentially more serious cardiovascular risks that will be emphasized in this article.

Prostaglandins cause vasodilatation of arterioles of glomeruli in the kidneys to maintain normal glomerular perfusion and glomerular filtration rate. Inhibition of prostaglandins leads to an unopposed constriction of the arterioles, which reduces the renal perfusion pressure and glomerular filtration rate. With these changes in renal hemodynamics and altered renal function, sodium and fluid retention may occur and HTN may be exacerbated, or HTN may occur in patients without previous HTN. More rare renal risks are interstitial nephritis, nephrotic syndrome, acute tubular necrosis, and acute renal failure.

Gastrointestinal adverse drug reactions include nausea, vomiting, dyspepsia, ulcer/bleed, and/or diarrhea. Approximately 50% of patients will show some mucosal damage to the small intestine, even with short-term therapy of NSAIDs. Indomethacin, ketoprofen, and piroxicam have the highest gastric adverse drug reactions and ibuprofen and diclofenac have lower rates of gastric adverse drug reactions. NSAIDs have both a direct and indirect irritation of the GI tract. Since these drugs are acidic molecules, they directly irritate the gastric mucosa. The inhibition of COX-1 and COX-2 enzymes leads to decreased levels of protective prostaglandins. This reduction in GI prostaglandins leads to increased gastric acid secretion, decreased mucus secretion, and decreased bicarbonate secretion. In Crohn's disease or ulcerative

colitis, NSAIDs should be rarely used due to the risk of gastric bleed and ulcers. Acetaminophen, which inhibits COX-2 in the central nervous system and very little in the rest of the body, to produce analgesia, is a much safer alternative in these patients with irritable bowel syndromes. Pain relievers with codeine may also be safer because they slow bowel activity.

Much of the new information regarding the cardiovascular risks of NSAIDs has come to light both professionally and publically in the past 10 years. Many of the published articles on NSAIDs safety before the mid-1990s, did not even mention cardiovascular risks other than renal effects and subsequent increase in blood pressure. After a study found that rofecoxib was associated with significant increases in the risks of MIs and CVAs, researchers began to question if other COX-2 selective NSAIDs might have the same risks. Rofecoxib was taken off the US market in 2004. Subsequent placebo-controlled trials demonstrated unequivocally that these selective COX-2 NSAIDs were associated with an increased risk of atherothrombotic vascular events. Clinicians and researchers then began to question if more traditional NSAIDs had similar cardiovascular risks. There were many meta-analyses of randomized, controlled trails of different NSAID medications soon to follow. Researchers were able to compare the different NSAIDs, in relation to cardiovascular risks, for common medications such as ibuprofen, naproxen, diclofenac, and celocoxib. Using innovative statistical methods, researchers were able to compare these medications even if they had never been studied head-to-head in the same clinical trial.

The largest meta-analyses study included 280 trials of NSAIDs versus placebo with more than 124,000 patients, and 474 trials comparing NSAIDs to one another with more than 229,000 patients. This study demonstrated that major vascular events were increased by about one-third with celecoxib or diclofenac versus placebo. Of 1,000 patients on celocoxib or diclofenac for 1 year, 3 more had major vascular events. Ibuprofen significantly increased the risk for major coronary events but not major vascular events. There were no increased risks of major coronary or major vascular events with naproxen. All NSAIDs were associated with a two-fold risk of heart failure in patients without a history of cardiac disease and a ten-fold risk of heart failure in patients with a cardiac history.

In patients with prior MI, NSAIDs are associated with an increased risk for death and recurrent MI. The use of NSAIDs is associated with a 45% increased risk for death or recurrent MI in first 7 days of treatment in patients with history of prior MI. After 3 months of treatment in these patients, the risk for recurrent MI or death increased to 55%.

Other risks or adverse drug reactions to NSAIDs include elevated liver enzymes, headache, and dizziness, fairly commonly. More uncommon risks include hyperkalemia, confusion, bronchospasm, rash, and Stevens-Johnson syndrome. Hematologic reactions include leucopenia, thrombocytopenia, and anemias. Allergic reactions are usually to one particular agent and not a class allergy. However, one in five patients will demonstrate a cross-reactive allergy.

NSAIDs are not recommended during pregnancy. They are not direct teratogens but do cross the placenta. They can produce premature birth and miscarriage in early pregnancy. In the third trimester, NSAIDs can produce premature closure of fetal ductus arteriosus and harmful renal effects in the fetus.

Any article on the risks of NSAIDs in podiatric medicine and surgery would be amiss if some discussion on the effects of NSAIDs on bone healing was not mentioned. There are many animal studies on this topic but few good human studies. Most animal studies show that NSAIDS have an inhibitory effect on fracture healing. The same finding is not confirmed in human studies. The few human studies that showed inhibition of healing of fractures, did not take smoking into account. Even studies with identical parameters have opposing results. There is no abundance of quality evidence from randomized controlled trials and the few randomized controlled trials available show that NSAIDs have no effect on bone healing. In a review of 316 papers, COX-2 inhibitors suppressed early fracture healing in animal studies but there was no evidence to substantiate the same finding in the human trials.

CONCLUSION

NSAIDs are commonly utilized in podiatric medicine and surgery. Many of the everyday conditions we treat are inflammatory and/or painful in nature. Physicians are often searching for other treatment regimens other than narcotic pain medications. With the historical risks of gastrointestinal adverse events and potential detrimental renal effects, physicians have used these medications cautiously. With the newer onslaught of data demonstrating now significant cardiovascular risks, our target patient population is again narrowed.

NSAIDs now are contraindicated in patients with coronary heart disease or history of CVA. Even low-dose short-term use of any NSAID is not recommended in patients with previous MI. They must be used with caution in patients with risk factors for coronary heart disease. If NSAID therapy is necessary in patients with cardiovascular disease, then naproxen less than 500 mg/day or ibuprofen less than 1,200 mg/day should be used for the shortest

period possible. Seven patient characteristics that increased the risk of adverse drug events with NSAIDs from more than 600 trials are as follows: age greater than 80, HTN, prior MI, prior cardiovascular disease including congestive heart failure and CVA, rheumatoid arthritis, chronic renal disease, and COPD.

In these at-risk patients, we must often look for other treatment modalities. Physical modalities such as heat or cold, exercise, weight loss, and formalized physical therapy are alternatives to oral NSAID therapy. Podiatric physicians also have the option of topical NSAIDs, which have demonstrated safety in at-risk patients no matter the age. We also have the treatment options of oral and injectable corticosteroids. If an oral course of NSAIDs is prescribed, then the lowest possible dose, of the least likely adverse event-producing NSAID, and for the shortest duration of time, should be used.

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