CE 2.0 ANCC Contact Hours

Nonsteroidal Anti-Inflammatory Drugs

Updates on Dosage Formulations and Adverse Effects

Kathleen Cunningham ▼ Danielle M. Candelario ▼ Lauren B. Angelo

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used medications due to their prescription and nonprescription availability, various dosage formulations, and therapeutic efficacy. Although NSAIDs have many known benefits, their effects on gastrointestinal, cardiovascular, bone, and renal physiology limit their widespread and long-term use. This article provides an update on dosage formulations, product availability, and pertinent adverse effects and warnings regarding the use of NSAIDs, with an emphasis on nonaspirin NSAIDs.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used and prescribed medication classes due to their analgesic, anti-inflammatory, and antipyretic properties. They were first described as a therapeutic class in the early 1960s after being recognized for their similarities to corticosteroids but were named as such to highlight their differences (Vane & Botting, 1998). Although NSAIDs are commonly used in clinical practice, it is important to weigh their benefits with the risks associated with a multitude of adverse effects.

Mechanism of Action and Pharmacokinetic Properties

NSAIDs exert their therapeutic and adverse effects largely via the inhibition of cyclooxygenase (COX) activity. COX is the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandin H_2, which is then metabolized into other prostaglandins (including prostaglandin E_2 [PGE_2]) and thromboxanes (Davies & Skjodt, 2000). There are two known isoforms of COX, COX-1 and COX-2. COX-1 is a constitutive enzyme that mediates gastrointestinal (GI) mucosal protection via increased blood flow, mucus, and bicarbonate secretion and increased epithelial growth to protect against gastric contents such as acid, pepsin, and bile salts. COX-1 also helps maintain platelet aggregation and vascular and renal homeostasis. COX-2 is an inducible enzyme released due to cytokine and inflammatory stimuli. Prostaglandin production via COX-2 thus mediates inflammation, pain, and fever, which explains why COX-2 is the desired target of NSAID activity (Chou et al., 2011).

There are more than 20 different NSAID products on the U.S. market, the majority of which are nonselective for the two COX isoforms (Clinical Pharmacology Database Online, 2020). Nonselective products have varying activity against COX-1 and COX-2, whereas coxibs or COX-2 selective NSAIDs are predominantly selective for COX-2 (see Table 1).

Most NSAIDs given orally are well absorbed in the GI tract and have high bioavailability. Topical NSAIDs sufficiently penetrate the skin barrier to provide therapeutic effect on joints and muscles. NSAIDs are highly protein bound (>90%), undergo hepatic metabolism, and are excreted in the urine (Davies & Skjodt, 2000).

Dosage Formulations and Availability

NSAIDs are available in multiple dosage forms including oral, intravenous, and topical formulations. Some require a prescription, whereas others do not. Dosage forms vary depending on the product and regulatory status. Table 1 lists those that are more commonly used or prescribed (Clincalc.com, 2020; Clinical Pharmacology Database Online, 2020). When comparing products that can be purchased without a prescription with those that require a prescription, there are some important safety considerations. The key differences are dosing and duration of use, which are both more conservative for nonprescription products. Self-treatment should be limited to acute conditions. When

Kathleen Cunningham, PharmD, BCPS, is Assistant Professor, Pharmacy Practice, College of Pharmacy, Rosalind Franklin University of Medicine & Science, North Chicago, IL; Clinical Pharmacist, Solid Organ Transplant, and Residency Program Director, PGY2 Solid Organ Transplant, Northwestern Memorial Hospital, Chicago, IL.

Danielle M. Candelario, PharmD, BCPS, is Associate Professor, Pharmacy Practice, College of Pharmacy, Rosalind Franklin University of Medicine & Science, North Chicago, IL.

Lauren B. Angelo, PharmD, MBA, is Associate Dean, Academic Affairs, and Associate Professor, Pharmacy Practice, College of Pharmacy, Rosalind Franklin University of Medicine & Science, North Chicago, IL.

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Correspondence: Kathleen Cunningham, PharmD, BCPS, Rosalind Franklin University of Medicine & Science, North Chicago, IL 60064 (kathleen.cunningham@rosalindfranklin.edu).

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Table 1. Commonly Prescribed Nonsteroidal Anti-Inflammatory Drugs

Generic Name	Common Brand Name(s)	Dosage Form(s)	Regulatory Status
Aspirin[a]	Bayer, Durlaza, Ecotrin	Tablet, chewable tablet, extended-release capsule, rectal suppository	Rx, OTC
Celecoxib[b]	Celebrex	Capsule	Rx
Diclofenac[a]	Voltaren	Capsule, tablet, extended-release tablet, ophthalmic drops, topical gel, topical patch, topical solution, solutions for injection	Rx, OTC (topical gel)
Ibuprofen[a]	Advil, Motrin	Capsule, tablet, chewable tablet, oral suspension, solution for injection	Rx, OTC
Indomethacin[a]	Indocin	Capsule, extended-release capsule, oral suspension, rectal suppository, solution for injection	Rx
Ketorolac[a]	Toradol	Tablet, ophthalmic drops, solution for injection, nasal spray	Rx
Meloxicam[c]	Mobic	Capsule, tablet, disintegrating tablet, oral suspension, solution for injection	Rx
Nabumetone[c]	Relafen	Tablet	Rx
Naproxen (base)[a]	Naprosyn	Tablet, extended-release tablet, oral suspension	Rx
Naproxen sodium[a]	Aleve, Anaprox, Anaprox DS	Tablet, liquid gel capsule	Rx, OTC

Note. Data from Clincalc.com (2020); Clinical Pharmacology Database Online (2020). COX = cyclooxygenase; OTC = over-the-counter (nonprescription); Rx = prescription only.
[a]Nonselective inhibitor of COX-1 and COX-2.
[b]Selective COX-2 inhibitor.
[c]Preferentially selective for COX-2.

patients are self-treating pain, they should consult a provider if the pain lasts more than 10 days. If they are self-treating a fever, a provider should be consulted if it lasts more than 3 days. Table 2 lists the self-care doses and maximum daily amounts, which are notably lower than when a patient is under a provider's care (Clinical Pharmacology Database Online, 2020).

A prescriber may make dosing recommendations for nonprescription products that extend beyond the Food & Drug Administration (FDA)-approved product label. Because there is provider oversight of the patient's treatment, this is an acceptable practice. As would be done with a prescription, the medication and dosing recommendations given to the patient should be documented.

Table 2. Dosing Differences Between Prescription and Nonprescription Nonsteroidal Anti-Inflammatory Drugs (Ages 12 Years and Older)

Medication	Nonprescription Oral Adult Dose; Maximum Daily Adult Dose	Prescription Oral Adult Dose; Maximum Daily Adult Dose
Ibuprofen	200–400 mg every 4–6 hours Max:1,200 mg per day	400 mg every 4–6 hours or 400–800 mg every 6–8 hours Max: 3,200 mg per day
Naproxen sodium	220 mg every 8–12 hours (may take 440 mg for the first dose) Max: 660 mg per day	275 mg every 8–12 hours or 275–550 mg every 12 hours Max: 1,100 mg per day

Note. Data from Clinical Pharmacology Database Online (2020).

When discussing self-care treatment options with patients, education on how to read nonprescription labels should be provided. If the product is not readily available to review with the patient, then the label information and warnings can be found on the manufacturer's website or dailymed.nlm.nih.gov. In addition to the dosing and safety warnings, it is important to check the active ingredients. Nonprescription NSAIDs are often combined with sedating antihistamines, decongestants, acetaminophen, and/or caffeine, depending on the conditions they are marketed to treat. Patients who consume these products unknowingly are not only overmedicating but also at increased risk for adverse effects from both the NSAID and the additional medication(s) in the combination product.

Adverse Effects

Gastrointestinal Effects of NSAIDs

Because of the inhibition of the COX-1 isoform, there are known consequences to NSAID use such as the effects on the GI system. When the protective prostaglandins are inhibited, NSAIDs are associated with direct GI irritation and mucosal injury, which can result in GI bleeding, perforation, the development of peptic ulcer disease, and dyspepsia. Risk factors for the development of NSAID-induced GI complications have been identified through case–control and cohort studies and should be referenced when determining appropriateness of NSAID therapy (Bhatt et al., 2008; Lanza et al., 2009).

Risk factors for NSAID-related GI complications include, but are not limited to:

- History of ulcer disease, ulcer complication, or GI bleed;
- High-dose NSAID use;
- Duration of NSAID therapy (events can occur within the first month, but ulcer risk decreases after the first few months of use);
- Concurrent use of alcohol, anticoagulants, corticosteroids, aspirin (including low-dose), or selective serotonin reuptake inhibitors; and
- Age 60 years or older.

In addition, risks of GI complications can be stratified by specific NSAIDs based on the COX-2 selectivity seen in vitro. NSAIDs with increased COX-2 selectivity (celecoxib, etodolac, meloxicam, nabumetone) are seemingly at a lowest risk for GI adverse effects; however, there is no strong evidence to suggest that GI events are lessened with COX-2 selective agents. Similarly, those with low to moderate COX-2 selectivity (indomethacin, ibuprofen, ketorolac, piroxicam) may carry a higher risk of GI injury (Lanza et al., 2009). Most evidence suggests that ibuprofen and celecoxib carry the lowest GI risk, naproxen is considered a moderate risk, and piroxicam and ketorolac have the highest risk. It is presumed that ibuprofen demonstrates the lowest risk due to nonprescription availability and lower dose usage. However, one meta-analysis found that ibuprofen administered at higher doses (up to 2,400 mg daily) resulted in a doubled risk of GI toxicity when compared with celecoxib and diclofenac (Bhala et al., 2013).

Individual patient risk assessment should be taken into consideration when determining whether NSAIDs can be safely used in patients at a high risk for GI complications. The American College of Gastroenterology has outlined a risk assessment strategy to select the most appropriate therapy based on both GI risk and cardiovascular (CV) risk. Patients at a low risk for GI events may safely use a low-risk NSAID (ibuprofen or celecoxib), whereas high-risk patients should avoid NSAIDs if possible or use a COX-2 selective agent (unless CV risk is elevated) and add on pharmacological mucosal protection (Lanza et al., 2009).

Cardiovascular Effects of Nonaspirin NSAIDs

The CV risk associated with NSAIDs was first identified when researchers found an increased risk of myocardial infarction in patients taking rofecoxib, a selective COX-2 inhibitor (Bombardier et al., 2000; Bresalier et al., 2005). This discovery ultimately led to the removal of rofecoxib from the U.S. market (U.S. FDA, 2004). In recent years, additional attention has been given to the increased risk for CV events with all nonaspirin NSAIDs, in particular myocardial infarctions and strokes.

Although the mechanism for this risk is not fully understood, there are several theories that have been explored and some seem to indicate that the degree to which COX-1 and COX-2 are inhibited is a factor (Patrono, 2016; Varga et al., 2017). Drugs with longer half-lives and ability to inhibit platelet aggregation via the COX-1 pathway may have less risk (Kearney et al., 2006). This explains why low-dose aspirin, which irreversibly inhibits platelet aggregation via the COX-1 pathway, does not carry this risk and is considered cardioprotective. Naproxen, when used in higher doses (500 mg twice daily), has a longer half-life and more sustained platelet inhibition than other nonaspirin NSAIDs and is comparable with aspirin in terms of its effect on thromboxane A_2 platelet activation (Kearney et al., 2006; Patrono, 2016). As such, high-dose naproxen has demonstrated less CV risk in some studies (Kearney et al., 2006; McGettigan & Henry, 2011; Trelle et al., 2011). However, not enough information currently exists to definitively state that one type of nonaspirin NSAID has more or less risk than another (U.S. FDA, 2015). With the possible exception of high-dose naproxen, the dose and duration of use should be considered. The higher the dose and the longer the NSAID is used, the greater the risk for CV events.

Increased Risk for Cardiovascular Disease

In addition to the COX-1 and COX-2 inhibiting properties of NSAIDs, there are other factors that may increase CV disease risk. Osteoarthritis (OA) has been implicated as a risk factor for CV disease. An analysis of 7,743 patients with OA compared with 23,229 patients without OA found that the risk of CV disease was significantly higher in the OA group (adjusted hazard ratio = 1.23; 95% confidence interval [CI] [1.17, 1.28]) (Atiquzzaman et al., 2019). Heart failure, ischemic heart disease, and stroke represented the highest CV disease risk among OA patients (42%, 17%, and 14%, respectively). The researchers found that this outcome was similar to previous findings. The researchers then sought to determine the role of NSAIDs in the CV risk in OA patients. It is not surprising the OA patients were much more likely to use NSAIDs (adjusted odds ratio [OR] = 5.09; 95% CI [4.33, 5.99]). Recognizing that other factors can contribute to CV disease in OA patients, the researchers adjusted for socioeconomic status, body mass index, hypertension, diabetes, hyperlipidemia, and the Romano comorbidity score. The hazard ratio of CV disease from NSAID use was 4.14 (95% CI [3.80, 4.50]) after these adjustments. NSAIDs contributed to 41% of the overall increased risk of CV disease in OA patients. Although the OA guidelines call for NSAID use in these patients (Bannuru et al., 2019; Kolasinski et al., 2020), the implications for CV disease risk should not be ignored.

Given that nonaspirin NSAIDs have been shown to increase the risk of hypertension, myocardial infarction, stroke, heart failure, and death due to coronary or vascular events (Coxib and traditional NSAID Trialists' [CNT] Collaboration, 2013; Kearney et al., 2006; Trelle et al., 2011), patients with or at risk for these conditions should use nonaspirin NSAIDs cautiously. Although CV events can occur in patients who lack these risk factors, the risk is greater in those who are already predisposed.

Cardiovascular Risk Warnings for Nonaspirin NSAIDs

Because data continue to emerge regarding the CV risks of nonaspirin NSAIDs, the warnings for both prescription and nonprescription products have been

strengthened and more prominently communicated to providers and patients. In July 2015, the U.S. FDA augmented its warnings on prescription labels for nonaspirin NSAIDs to reflect the increased risk for myocardial infarction or stroke (U.S. FDA, 2015). These warnings state that these risks are possible within the first weeks of using an NSAID and may increase the longer the NSAID is used. Higher NSAID doses lead to a greater risk. The risk may be evident even in patients who do not have heart disease or risk factors for heart disease. However, these conditions place patients at a higher risk. The label warning also notes that after a first myocardial infarction, patients treated with NSAIDs were more likely to die in the first year than those who did not take NSAIDs. In addition, heart failure risk is increased with NSAID use. The medication guides that the FDA requires to be dispensed with all nonaspirin NSAID prescriptions also include these warnings but in patient-friendly terminology (U.S. FDA, 2016).

Shortly after the prescription label updates, the FDA mandated label changes for nonprescription nonaspirin NSAIDs to place greater emphasis on myocardial infarction and stroke risk (Pfizer Consumer Healthcare, 2016). The labels now state, "NSAIDs, except aspirin, increase the risk of myocardial infarction, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed." The nonprescription labels and medication guides are intended for patients to use and understand. It is the healthcare provider's responsibility to supplement the information contained in the written warnings by educating patients on the CV risks and warnings of nonaspirin NSAIDs.

Effects on Renal Homeostasis

NSAIDs are associated with various effects on renal function including acute kidney injury, electrolyte imbalances, and acute interstitial nephritis. Risk factors for kidney injury in patients using NSAIDs include chronic kidney disease, hypovolemia, and concurrent medications (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) (Lapi et al., 2013; Schlondorff, 1993). COX-2 is constitutively expressed in the kidneys and through NSAID-induced COX inhibition, prostaglandin synthesis is impaired. Although prostaglandins do not have a significant role in renal homeostasis in patients with normal kidney function, in the setting of vasoconstriction, prostaglandins mediate vasodilation to preserve renal blood flow and glomerular filtration rate. Therefore, the inhibition of prostaglandins may negate these protective mechanisms (Schlondorff, 1993). Inhibition of prostaglandin synthesis may also result in electrolyte disturbances as prostaglandins mediate renin, aldosterone, and antidiuretic hormone (ADH) synthesis (Oates et al., 1988). With decreased renin and aldosterone secretion, potassium excretion is decreased and hyperkalemia may result. The inhibition of ADH secretion will result in decreased free water excretion, increasing the risk for hyponatremia and edema.

Because of the aforementioned risks, patients are generally recommended to avoid nonaspirin NSAIDs in the setting of chronic kidney disease and to use alternative medications for pain and fever management. If NSAID therapy is required with an extended duration of use, renal function and electrolytes should be closely monitored prior to and throughout treatment.

Effects on Bone Healing

With some exceptions, NSAIDs are considered safe and effective when used appropriately and for the shortest duration possible. As such, NSAIDs are commonly used as single analgesics for minor procedures or as a component of a multimodal analgesic approach for the treatment of postoperative pain in adults. NSAIDs in conjunction with opioids are associated with less postoperative pain or opioid consumption than opioids alone (Chou et al., 2016). Despite their benefit, providers may avoid these medications because of the possible impact on bone healing (Wheatley et al., 2019).

Mechanism of Bone Healing

The process of bone healing is complex and influenced by multiple factors. A number of nonmodifiable risk factors include age, sex, nutritional status, and smoking, whereas other risk factors may be influenced by the patient and therapeutic regimen (Cosmo & Congedo, 2015; Wheatley et al., 2019). As part of the therapeutic regimen, NSAIDs have been identified as one potential risk factor, although the evidence and data are conflicting.

The exact mechanism by which NSAIDs affect bone healing is not fully elucidated, although most studies believe it is closely related to their propensity for COX-2 inhibition. Bone healing is a complex cascade of coagulation and inflammatory responses that enable the healing of bone trauma or fractures. Following a fracture, there is a release of prostaglandins as a result of an acute inflammatory response; COX-2 also plays a critical role in this acute stage through its induction of osteoblast activity. NSAIDs' interference with COX-2 regulation and subsequent inhibition of prostaglandin, more specifically PGE_2, is thought to be the mechanism through which bone healing is delayed (Dodwell et al., 2010; Wheatley, 2019). Angiogenesis, or the development of new blood vessels, is also crucial for the response to injury. It is speculated that NSAIDs affect angiogenesis as well, resulting in the inhibition of blood vessel synthesis, which may contribute to slowing down the healing process (Lisowska et al., 2018).

Evidence of NSAID Effect on Bone Healing

The mechanism and potential of NSAIDs to delay bone healing have been demonstrated in both in vitro and animal studies; indomethacin, naproxen, and celecoxib are the drugs most commonly reported in studies. As early as 1976, Bo et al. reported an impaired healing of nonimmobilized femoral fractures in rats when given oral indomethacin. More recently, Simon and O'Connor (2007) found evidence that COX-2 selective therapy with celecoxib within 14 days after the fracture increased the proportion of nonunions in their animal model. Several other animal studies have supported a similar result (Dimar et al., 1996; Gerstenfeld et al., 2003; Kidd et al., 2013).

The evidence in humans is less clear. Studies are much more variable in their conclusions as to whether NSAIDs are beneficial or not. These conflicting results are due to several factors such as the evaluation of different types of surgery and the retrospective study designs (Cosmo & Congedo, 2015). Per a meta-analysis in 2010, Dodwell et al. noted a difference in results when evaluating lower quality versus higher quality studies. A significant association between lower quality studies and higher reported ORs for nonunion was observed. However, there was no increased risk of nonunion with NSAID exposure when only the highest quality studies were assessed (Dodwell et al., 2010). A more recent meta-analysis by Wheatley et al. in 2019 evaluated 16 studies of more than 15,000 patients. A total of 512 cases of delayed union or nonunion incidents were reported, of which 226 had NSAID exposure. In these patients, the risk of delayed union or nonunion incidents was higher than that in non-NSAID users (OR = 2.07; 95% CI [1.19, 3.61]). These conflicting conclusions are representative of the disparity of data linking NSAIDs to an effect on bone healing.

Clinical Considerations for NSAIDs and Bone Healing

In the 2016 clinical guidelines, the American Pain Society recognized the possible association between high-dose NSAID use and nonunion in animal studies (Chou et al., 2016). However, in the absence of high-quality evidence in orthopaedic surgery, insufficient evidence was found to recommend against the use of NSAIDs in patients who undergo surgery for orthopaedic fractures. The guidelines acknowledge the uncertainty of potential harms and that the decision to treat with NSAIDs should be through a shared clinical decision-making process with the patient and the provider. To date, the American Pain Society has made no further statement or guideline updates. NSAIDs should be utilized judiciously as part of the multimodal pain management in the postoperative setting weighing the potential impact on nonunion and the need for alternative pain control with opioids.

Conclusion

NSAIDs are easily accessible and widely used. Healthcare providers need to be aware of the many untoward effects associated with their use. A risk versus benefit evaluation should be implemented when determining the appropriate product, dose, and duration of NSAID use. Patient education is also a critical component to the safe and effective use of NSAIDs.

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