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# A Review of Nonsteroidal Anti-Inflammatory Drugs

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*It is essential that nurse anesthetists are aware of the potential side effects and interaction of drugs that patients are taking before administering an anesthetic. Among the most commonly taken medications are nonsteroidal anti-inflammatory drugs (NSAIDs). Because these drugs have become almost ubiquitous, there is a risk of underestimating potential effects, which may be harmful for the patient undergoing anesthesia and surgery. These effects can range from mild to severe and can be exacerbated by drug interactions with many commonly administered medications. This review of NSAID pharmacology and interactions is intended to serve as an update and refresher for nurse anesthetists to increase their awareness of the potential untoward effects of postoperative bleeding, gastrointestinal bleeding, asthma, hepatic and renal toxicity, and cardiovascular events.*

***Keywords:*** Adverse drug effects, drug interactions, nonsteroidal anti-inflammatory drugs.

## Objectives

At the completion of this course, the reader should be able to:

1. Describe the mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs).
2. List the common adverse effects of NSAID therapy.
3. Differentiate characteristics of NSAIDs by classification.
4. Discuss the common potential drug interactions and their mechanisms associated with NSAID therapy.
5. Describe the NSAID pharmacokinetic and pharmacodynamics considerations as they relate to intraoperative.

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently administered drugs by prescription or over-the-counter. They are administered for their anti-inflammatory, analgesic, and antipyretic properties. Certified Registered Nurse Anesthetists (CRNAs) must be aware that many patients using NSAIDs may also be concomitantly taking other prescribed medications that may result in drug interactions with serious consequences. Interactions from NSAIDs can occur with antihypertensive medications, antithrombotic medications, drugs to treat heart failure, systemic glucocorticoids, and selective serotonin reuptake inhibitor antidepressants (SSRIs).[1]

As analgesics, NSAIDs offer the advantage of reducing or avoiding the harmful effects of opioids, but they are not without untoward effects of their own. Drug interactions and untoward effects of NSAIDs are often a direct result of their effect on normal physiologic activity.[2] To understand these effects, it is important to review the normal process of the inflammatory response and the mechanism by which NSAIDs alter it.

## Eicosanoid Formation

Eicosanoids are fatty acid derivatives produced in cell membranes from arachidonic acid. Subgroups of eicosanoids form based on the enzyme pathways with which they are acted on, such as the enzyme cyclooxygenase (COX) to produce prostaglandin, prostacyclin, and thromboxane or the enzyme lipoxygenase to produce leukotriene and hydroxyl derivatives (Figure). These substances play a role in normal physiologic processes and in response to pathophysiologic stimuli or as part of the immune response to invading organisms or antigens.[3]

## Cyclooxygenase Pathway

Cyclooxygenase exists in several forms; however, those most commonly discussed and studied are COX-1 and COX-2. The prostaglandins formed by reactions through COX-1 are important for a variety of normal physiologic processes such as gastrointestinal and renal protection, macrophage differentiation, and platelet aggregation. By comparison, COX-2 is found mainly in inflammatory and

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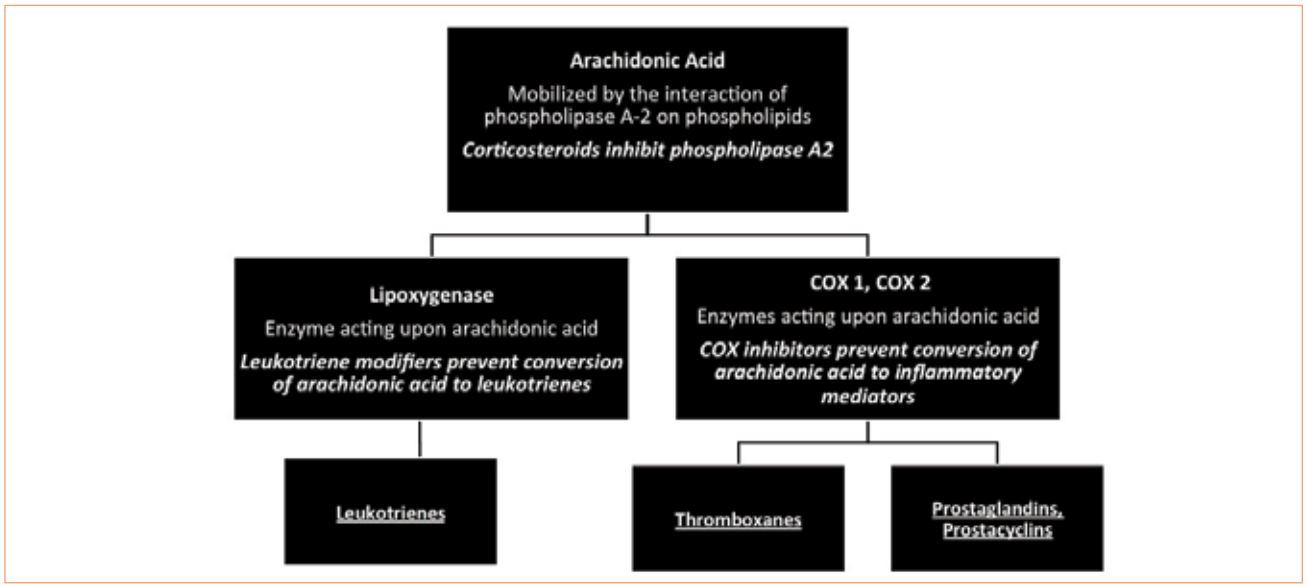


**Figure.** Eicosanoid Synthesis: Formation of Mediators of Inflammation[3,4]
Abbreviation: COX, cyclooxygenase.

immune cells and is expressed through specific stimuli, such as cytokines and other inflammatory mediators. It is active at sites of injuries and promotes the response of inflammation, fever, pain, and carcinogenesis.[2-4]

## Selective and Nonselective Cyclooxygenase Inhibition

Inhibition of COX activity by NSAIDs results in therapeutic and untoward effects. The use of both selective and nonselective NSAIDs has been demonstrated to be effective in the management of postoperative pain. The advantages of their therapeutic effects are summarized in Table 1.[2,4-6] The untoward effects of nonselective NSAIDS are primarily related to the inhibition of the normal physiologic functions of COX 1 (Table 2).[1,4,7-9] Many of these effects are dose dependent.[5]

Selective inhibitors of COX-2 are thought to lack the effects on normal physiologic function seen with the nonselective NSAIDs. Evidence shows that COX-2 selective drugs reduce the risk of formation of NSAID-induced gastric ulcers compared with nonselective NSAIDs.[6] However, selective COX-2 inhibitors have been associated with an increased risk of cardiovascular side effects, including myocardial infarction and worsening of preexisting conditions such as congestive heart failure and hypertension.[7] The use of nonselective NSAIDs has been associated with an increased risk of postoperative bleeding related to COX-1 platelet inhibition, whereas the use of COX-2 selective NSAIDs have been shown to be efficacious for analgesia without increasing bleeding risk.[5]

## Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs

The most worrisome side effects of NSAIDs are the result of platelet inhibition, inhibition of prostaglandin formation needed for normal gastrointestinal and renal function, cardiotoxicity and hepatotoxicity, and drug-induced asthmatic responses. These effects are extensions of the pharmacodynamics of the drug and may be worsened by drug interactions.

- Reduce the activation and sensitization of peripheral pain receptors
- Reduce inflammatory response
- No dependence or addiction potential
- Synergistic effects with opioids (opioid-sparing effect)
- Used as part of multimodal analgesia ("WHO Ladder")
- Useful for preemptive analgesia and pain prophylaxis (decreased postoperative pain)
- No respiratory depressant effects
- Causes minimal or no nausea and vomiting compared with opioids
- Long duration of action
- Less dose variability than opiates
- More effective than opioids for some pain types (ie, bone pain, pain during movement)
- No central effects such as sedation or papillary changes

**Table 1.** Therapeutic Effects of Cyclooxygenase Inhibitors[2,4-6]
Abbreviation: WHO, World Health Organization.

• ***Platelet Inhibition.*** The extent and duration of the anticoagulation effect varies by drug. Platelet inhibition from most NSAIDs is reversible but typically lasts longer than the drug's termination half-life. Aspirin causes irreversible inactivation of platelet COX-1, and its effects last for the life of the platelet (8-10 days).[6] Surgical and anesthetic implications of NSAID-induced antiplatelet

| System | Reported adverse effects |
|---|---|
| Gastrointestinal | • Discomfort, nausea, and diarrhea<br>• Peptic ulceration<br>• Gastrointestinal bleeding may occur<br>• Induction or exacerbation of colitis |
| CNS-related | • Headache,<br>• Vertigo, dizziness, tinnitus<br>• Nervousness<br>• Depression, drowsiness<br>• Insomnia |
| Hypersensitivity reactions | • Fever, angioedema, bronchospasm, and rashes<br>• Hepatotoxicity, aseptic meningitis occur rarely |
| Hematologic | • Anemia, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis |
| Renal | • Nephrotoxicity (interstitial nephritis, nephrotic syndrome)<br>• Renal failure or impairment<br>• Hematuria<br>• Long-term use or abuse has been associated with nephropathy<br>• Fluid retention |
| Cardiovascular | • Elevated blood pressure<br>• Heart failure<br>• Thrombotic events<br>• May negate beneficial cardiac effects of aspirin |
| Other and rare adverse effects | • Photosensitivity<br>• Alveolitis, pulmonary eosinophilia<br>• Pancreatitis<br>• Stevens-Johnson syndrome<br>• Toxic epidermal necrolysis |

**Table 2.** Reported Adverse Effects of Nonsteroidal Anti-inflammatory Drugs by Body System[1,4,7-9]
Abbreviation: CNS, central nervous system.

functions include the risk of postoperative bleeding as well as hematoma formation from neuraxial anesthesia techniques when combined with anticoagulant drugs. The appropriate diagnostic test is bleeding time, as opposed to platelet count, because the activity of platelets and not their quantity is affected.[10]

• ***Gastrointestinal.*** Gastrointestinal effects of NSAIDs can range from dyspepsia to gastric ulceration and perforation. Symptoms such as dyspepsia, nausea, and abdominal pain occur in 15% to 40% of patients taking NSAIDs. More severe effects such as ulceration occurs in 5% to 20% of NSAID users, and 1% or 2% will experience bleeding and perforation.[6]

A retrospective study of more than 13,000 patients undergoing nonelective colorectal surgery involving colon anastomosis concluded that NSAIDS are associated with a significant risk of postoperative anastomotic leaks. Although the study does have limitations, the authors cite other small studies suggesting similar outcomes and make a call for the need for further research.[11]

• ***Cardiovascular.*** The COX-2 inhibitor drugs have been associated with an increased risk of stroke and myocardial infarction, exacerbations of preexisting congestive heart failure, and worsening of hypertension. In addition, interference with the cardioprotective effects of aspirin has been noted during simultaneous administration of other NSAIDs.[6,7] The selective COX-2 inhibitor rofecoxib (Vioxx) was associated with a significant increase in the rate of cardiovascular disease, which led to its removal from the market. The mechanism for this risk is unclear and prompted some to focus primarily on the cardiovascular effects associated with selective COX-2 inhibition; however, there is also evidence for concern related to the use of nonselective NSAIDs.[7,12]

• ***Renal.*** Inhibition of COX-1 depresses prostaglandin activity that is critical for renal cell integrity. Although COX-2 selective drugs minimize adverse effects on the gastrointestinal system and platelets, cardiac and renal concerns still exist.[8] Except in cases of high-dose administration of NSAIDs, this inhibition of prostaglandin synthesis is reversible so that the likelihood of renal toxicity is rare; however, the risk increases greatly in patients with coexisting renal disease. Risk factors for the development of NSAID-induced acute renal failure include advanced age, hypovolemia, renal or hepatic disease, sepsis, congestive heart failure, and major surgery.[1,6,8] It is important to consider that NSAID-induced decreases in renal function may influence therapeutic levels of

other drugs reliant on renal elimination.[6]

• ***Asthma Response.*** Some patients receiving NSAIDs may demonstrate aspirin intolerant/induced asthma (AIA). Inhibition of COX-1 by NSAIDs other than aspirin has also been associated with AIA. The incidence of AIA is relatively low in the general adult nonasthmatic population, estimated at 4%, but it may be as high as 8% to 12% in patients with preexisting asthma.[13] The cause of AIA is theorized to be related to COX-1 inhibitory effects on prostaglandin synthesis rather than an allergic response. Although case reports suggest otherwise, COX-2-selective NSAIDs have been shown to be safe in patients with AIA.[14,15]

## Effects on Bone Healing

The role of COX-2 in bone healing has been well discussed in the literature. Data suggest that inducible COX-2 plays an important role in bone formation.[16,17] Many studies have suggested that the use of NSAIDs may inhibit bone healing. These effects may vary based on drug and doses used as well as the specific discussion as it relates to bone fracture, regeneration, or fusion.[18] For this reason orthopedic surgeons may have specific preferred practices related to the use of NSAIDs for postoperative pain management in their patients undergoing joint replacement, fusions, or fracture reduction. Further research may be warranted to determine best prescribing practices.

## Classifications of Nonsteroidal Anti-Inflammatory Drugs

• ***Aspirin.*** Aspirin is a nonselective COX inhibitor and is derived from the acetylation of salicylic acid.[6] The primary adverse effects most often associated with aspirin are gastrointestinal, although excessive bleeding and renal effects can occur with higher doses.[19]

Various benefits from aspirin have been suggested, including oncologic protection, but the more popular use of aspirin is based on benefits from its antiplatelet action.[19-21]

Unlike other NSAIDs whose effects on platelets reverse on removal of the drug, aspirin irreversibly inhibits platelet function. This effect has been used therapeutically to prevent thromboembolism and extensively for preventing coronary events. It has been suggested, however, that COX-2 inhibition by either selective or nonselective NSAIDs can be associated with an increase in cardiovascular risk.[22] When considering the accepted protective value of aspirin, this would seem contradictory, yet in some studies aspirin has been shown to increase cardiovascular risk and the cardioprotective benefits of low-dose aspirin therapy have been shown to diminish when aspirin is taken concomitantly with other NSAIDs.[6,22]

Aspirin combined with nonselective NSAIDs increases the risk of adverse gastrointestinal effects and negates the gastrointestinal protective effects of selective NSAIDs.[4,22] As with other NSAIDs, aspirin provides additive anticoagulant effects to warfarin and other anticoagulant drugs.[22]

• ***Propionic Acid Derivatives.*** Ibuprofen, ketoprofen, and naproxen are well-known propionic-derivative NSAIDs. Ibuprofen is typically prescribed for its analgesic properties. The combination of NSAIDs with opioid analgesics is common. The propionic acid derivatives have been shown to synergistically potentiate the analgesic properties of hydrocodone and oxycodone significantly while having minimal benefit when combined with fentanyl or morphine. This synergy is not seen with aspirin or ketorolac when combined with hydrocodone and oxycodone.[23,24]

Ibuprofen is associated with the well-known adverse effects of the nonselective NSAID class. Gastrointestinal tract irritation and bleeding are described as the 2 most common side effects. Bleeding tendencies can be of concern because of ibuprofen's interference with platelet aggregation through inhibition of thromboxane $A_2$. As with other NSAIDs, there is a potential for additive effects when administered along with anticoagulants.[10,25]

Intravenous ibuprofen (Caldolor) is an alternative for NSAID administration in the perioperative setting, where the use of the oral route may be contraindicated (Table 3).[26-28] The concerns related to drug interactions and potential adverse effects as well as contraindications for intravenous ibuprofen are similar to those seen when administered orally.[29,30]

• ***Ketorolac.*** Ketorolac is a commonly used, nonselective COX inhibitor NSAID for the management of postoperative pain and is frequently administered via parenteral routes in the operating room (see Table 3). It is known to be an excellent analgesic, having only moderate anti-inflammatory properties. Its adverse reactions include those previously discussed for the nonselective NSAIDs. Its use is best limited to 5 days' duration because of significant risk of renal impairment and peptic ulceration from prolonged administration.[26] Ketorolac has been shown to have synergistic analgesic effects when combined with morphine and when combined with intrathecally administered clonidine.[23,31] Ketorolac is metabolized in the liver and is 99% protein bound. Its drug interactions are similar to most NSAIDs but can be extensive. Ketorolac is contraindicated in women in labor because it may inhibit uterine contractions. It may also affect uterine circulation and is eliminated in breast milk.[26] The antihypertensive effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists as well as the effects of diuretics may be decreased by ketorolac. The platelet inhibition of ketorolac may result in additive bleeding effects with the use of warfarin and other anticoagulant drugs.[7,26]

• ***Acetaminophen.*** Acetaminophen (also known as paracetamol) was introduced for medical use in 1893.

| Characteristic | Ketorolac (Toradol) | Acetaminophen (Ofirmev) | Ibuprofen (Caldolor) |
|---|---|---|---|
| IV Dosing and administration | IV infusion should be administered rapidly.<br>*< 65 years of age:* 30 mg in single dose or every 6 hours in multiple-dose therapy not to exceed 5 days<br>*> 65 years of age or < 50-kg patient in weight:* 15 mg | Only as a 15-minute infusion single or repeated dose (minimum interval, 4 hours)<br>*Adults and adolescents: > 50* kg-1,000 mg every 6 hours or 650 mg every 4 hours. Not to exceed 4000 mg/d.<br>*Children > 2-12 years*: 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours to a maximum of 75 mg/kg/d. | Must be diluted before IV infusion to concentration of 4 mg/mL or less.<br>*Pain:* 400 mg-800 mg IV over 30 minutes every 6 hours as needed<br>*Fever:* 400 mg IV over 30 minutes followed by 400 mg every 4 to 6 hours or 100 mg-200 mg every 4 hours |
| Pharmacokinetics/ dynamics | NSAID analgesia believed to be related to prostaglandin synthesis inhibition.<br>Peak effect 2-3 hours; 99% protein bound. Metabolized in liver, eliminated in urine (60% unchanged).<br>Terminal half-life of 30-mg dose = 5.6 hours. | Precise mechanism of action is not established; believed to primarily involve central actions.<br>10%-25% protein bound. Metabolized in the liver through conjugation and oxidation. Intermediate metabolite NAPQI. Eliminated in urine < 5% as unconjugated (free) acetaminophen.<br>Terminal half-life = 2.4 hours in adults, 3.0 hours in children, 4.2 hours in infants, and 7.0 hours in neonates. | NSAID analgesia, anti-inflammatory, and antipyretic effects believed to be related to prostaglandin synthesis inhibition.<br>99% protein bound. Metabolized in liver, eliminated mainly in urine and also bile.<br>Terminal elimination half-life = 2.22 hours (400 mg) or 2.44 hours (800 mg). |
| Indications | Acute pain | Mild to moderate pain, moderate to severe pain with adjunctive opioid analgesics, reduction of fever | Mild to moderate pain, moderate to severe pain with adjunctive opioid analgesics, reduction of fever |
| Contraindications | • Hypersensitivity to ketorolac<br>• See boxed warning topics<br>• Labor and delivery<br>• Concomitant use with probenecid or pentoxifylline<br>• In patients concurrently receiving aspirin or NSAID therapy<br>• "Should not" be given to patients who have experienced asthma, urticaria, or allergic-like reactions after taking aspirin or other NSAIDs | • Hypersensitivity to acetaminophen<br>• Patients with severe hepatic impairment or severe active liver disease | • Hypersensitivity to ibuprofen<br>• See boxed warning topics<br>• Asthma, urticaria, or allergic-like reactions after taking aspirin or other NSAIDs |
| Approved in pediatrics | Not indicated. No data to support use in pediatric patients. | Yes | Not indicated. No data to support use in pediatric patients. |
| Boxed warning topics | *Cardiovascular:*<br>Increased risk of thrombotic events, MI, and stroke; contraindication in perioperative CABG surgery<br>*Gastrointestinal:*<br>Bleeding, ulceration, and perforation<br>*Renal:*<br>Contraindicated in patients with advanced renal impairment and those at risk of renal failure because of volume depletion<br>*Bleeding:*<br>Contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis, and those at high risk of bleeding | *Dosing:* Use with other acetaminophen-containing products; *association with acute liver failure* | *Cardiovascular:*<br>Increased risk of thrombotic events, MI, and stroke; contraindication in perioperative CABG surgery<br>*Gastrointestinal:*<br>Bleeding, ulceration, and perforation |

**Table 3.** Comparison of Available Intravenous Nonsteroidal Anti-inflammatory Drugs[26-28]
Abbreviations: CABG, coronary artery bypass graft; IV, intravenous; MI, myocardial infarction; NAPQI, *N*-acetyl-P-benzoquinone imine; NSAID, nonsteroidal anti-inflammatory drug.

The exact mechanism of action is unknown, and its categorization as an NSAID is debatable because it has little anti-inflammatory effect. This is believed to be related to its minimal capacity to inhibit peripheral prostaglandin synthesis. Acetaminophen is thought to act more centrally than peripherally. Suggested theories of the mechanism of action include COX inhibition; activation of the endogenous opioid path; or interactions with nitric oxide, cannabinoid, or serotonin functions. It is believed to offer antipyretic effects through the inhibition of the central hypothalamic heat-regulating center.[32]

In contrast to traditional NSAIDs, acetaminophen is only 20% to 50% protein bound. As a result, the theoretical concern of high protein binding and its role in drug interactions may be minimized. Acetaminophen is metabolized in the liver and eliminated in the urine.[9]

In low and therapeutic dosing, acetaminophen has been shown to cause fewer side effects or adverse reactions compared with traditional NSAIDs. Acetaminophen has not been shown to cause antiplatelet activity or gastric irritation; however, acetaminophen may potentiate the anticoagulant effect of warfarin, requiring closer monitoring of coagulation parameters.

This interaction may be the result of a pharmacokinetic interaction at the level of the cytochrome P-450 (CYP) 2C9 system causing a decrease in warfarin metabolism or through a toxic metabolite causing inhibition of the enzymes of the vitamin K. Also, acetaminophen-induced hepatotoxicity may interfere with warfarin metabolism.[33]

Acetaminophen toxicity is a major cause of acute hepatoxicity.[34] Liver damage has been reported as a result of acetaminophen toxicity, particularly following excessive dosing. The mechanism of this damage is not through the parent compound but rather its toxic metabolite, *N*-acetyl-P-benzoquinone imine (NAPQI). The risk of toxicity is heightened in patients who are genetically predisposed and in those using ethanol long term or concomitantly using phenytoin, isoniazid, or the retrovirus medication ritonivir.[35] Additionally, barbiturates may increase the risk of acetaminophen hepatotoxicity by inhibiting acetaminophen glucuronidation, resulting in further metabolism through oxidation.[36] Pharmacologic management of acetaminophen-induced hepatotoxicity includes the administration of *N*-acetylcysteine, which serves to replenish glutathione stores.[32] Some concern has been proposed that children are at an increased risk of hepatic toxicity; however, the literature does not clearly support those claims.[36]

Acute renal failure has also been described because of acetaminophen toxicity and has been associated with chronic renal failure in some cases. The mechanism is poorly understood; however, the overproduction of nitric oxide has been implicated, as have the theories that a collection of the toxic metabolite p-aminophenol may lead to medullary necrosis or that prostaglandin synthesis inhibition may cause medullary ischemia.[37] Some evidence exists to suggest that acetaminophen or aspirin does not increase the rate of progression of chronic renal disease and may be administered in therapeutic doses to patients with chronic renal insufficiency.[38] Because these adverse effects are typically associated with advanced doses in excess of 4 g/d, the practitioner must consider the patient's use of acetaminophen and acetaminophen-opioid compounds when calculating safe dosage ranges.[35]

Historically acetaminophen has been available only through oral and rectal routes. Intravenous acetaminophen (paracetamol) has been available in Europe since 2002 but more recently has been introduced and approved in the United States (see Table 3). Intravenous acetaminophen (Ofirmev) has been shown to provide greater analgesic efficacy than placebo while significantly reducing opioid need.[39,40] Side effects appear to be limited to local reactions, with systemic concerns similar to those with oral administration.[40,41]

## Drug Interactions With Nonsteroidal Anti-Inflammatory Drugs

Table 4 summarizes the NSAID-drug interactions,[9,15,26,42] which are described in detail here.

• ***Anticoagulants.*** Because of the inherent effect of COX inhibition on platelet function, it is not surprising that traditional NSAIDs such as aspirin, ibuprofen, and ketorolac interact with other drugs that have anticoagulation properties by exacerbating this effect. This has been well studied in the case of warfarin inhibition of vitamin K-dependent clotting factors as well as antiplatelet anticoagulation drugs.[22,43] Warfarin has been frequently described as vulnerable to drug interactions because of its low therapeutic index (narrow margin of safety). Besides the additive effects of anticoagulation through their respective mechanisms of action, warfarin potentiation by NSAIDs may occur as a result of a displacement from their protein-binding sites.[42] Acetaminophen has not been found to inhibit platelet activity, but it has been shown to potentiate the effects of warfarin, suggesting the need for closer monitoring when the drugs are given concomitantly.[33]

• ***Antihypertensive Agents.*** Studies suggest an association between the presence of hypertension and the use of NSAIDs. It has been questioned whether NSAID use causes an increased risk of hypertension, minimizes the effects of antihypertensive medicines, or worsens the baseline state of hypertension or congestive heart failure.[1] Nonsteroidal anti-inflammatory drugs may increase blood pressure through inhibition of certain vasodilator prostaglandins such as $PGE_2$ and $PGI_2$. Other possible explanations include sodium retention seen in approximately 25% of NSAID users or through the production of vasoconstrictive substances produced when arachidonic acid is metabolized in the presence of COX inhibition.[44] In

| Nonsteroidal anti-inflammatory drug | Drugs causing increased levels or effects | Drugs causing decreased levels or effects |
|---|---|---|
| Acetaminophen | Warfarin | |
| Aspirin | • Anticoagulant drugs | • ACE inhibitors |
| | • Antiplatelet drugs | • Loop diuretics |
| | • Carbonic anhydrase inhibitors | • NSAIDs decrease cardioprotective effect of aspirin |
| | • Methotrexate | |
| Ibuprofen, ketorolac | • Aminoglycosides | • ACE inhibitors |
| | • Anticoagulant drugs | • Angiotensin II antagonists |
| | • Antiplatelet drugs | • β-Antagonists |
| | • Lithium | • Hydralazine |
| | • Potassium-sparing diuretics | • Loop diuretics |
| | • Methotrexate | • Salicylates |
| | • Nondepolarizing muscle relaxants | • Thiazide diuretics |
| | • NSAIDs | |

**Table 4.** Summary of Drug Interactions With Nonsteroidal Anti-inflammatory Drugs[9,15,26,42]
Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drug.

addition, NSAIDs have been shown to decrease the levels and/or effects of several classes of antihypertensive agents, including ACE inhibitors, angiotensin antagonists, and β-receptor antagonists.[1,44,45] Calcium channel blockers and β-antagonists may be affected to a lesser extent. Additionally, NSAID effects on renal prostaglandin may affect sodium and water transport actions of diuretics, thereby decreasing their actions.[6,46]

Unlike other NSAIDs, aspirin does not appear to cause an increase in blood pressure because of the specific prostaglandins affected.[42] Acetaminophen is frequently recommended as an analgesic or antipyretic for patients with hypertension; however, evidence suggests that acetaminophen can also increase blood pressure in patients with coronary artery disease.[47]

• ***Ethanol.*** The primary concern with ingestion of ethanol and NSAIDs is an increased risk of gastric and duodenal ulcer formation and gastric bleeding because of the additive properties of both substances. Additionally, ethanol may stimulate gastric acid secretion, worsening the gastric mucosal effects of NSAIDs.[42] Long-term or excessive ethanol intake can result in an increased risk of acetaminophen toxicity. This may be the result of ethanol's role as an inducer of the CYP450 substrate CYP2E1, causing an increase in the acetaminophen metabolite NAPQI through depletion of glutathione, needed for NAPQI metabolism.[35]

• ***Antidepressant Drugs.*** Selective serotonin reuptake inhibitors are widely prescribed for a variety of psychiatric disorders and other illnesses and symptoms. The inhibition of serotonin reuptake by this class of drugs is not limited to reuptake mechanisms in the central nervous system but also inhibition in platelets. The release of serotonin is an important component in platelet aggregation such that it has been suggested that SSRIs may increase the risk of bleeding.[42,48] There is evidence to suggest that SSRIs may produce an additive or synergistic affect when combined with other drugs that increase the likelihood of bleeding, including NSAIDs, although some studies suggest these effects are not clinically significant.[42,49,50]

The use of NSAIDs with tricyclic antidepressant drugs does not appear to be associated with an increased risk of bleeding or other side effects.[42,50] Monoamine oxidase inhibitors are known to interact with many classes of drugs; however, NSAIDs appear to be safely used with them.[50]

Nonsteroidal anti-inflammatory drugs have been demonstrated to cause a significant increase in serum lithium levels. This has been attributed to NSAID-induced inhibition of renal prostaglandin synthesis and the resultant decrease in renal elimination of lithium. Lithium has been described as a drug with a low therapeutic window, and as such it is recommended that levels be monitored closely if these drugs are coadministered.[42]

• ***Use of Multiple Nonsteroidal Anti-inflammatory Drugs.*** Most of the common concerns regarding the concomitant use of NSAIDs from differing classes are the result of compounding of the expected side effects; however, some specific phenomena have been noted. The cardioprotective benefits of low-dose aspirin therapy have been shown to diminish when it is taken with other NSAIDs.[6,22] Nonselective COX inhibitors negate the gastrointestinal protective effects of COX-2 selective drugs.[4,22] Nonselective NSAIDs increase the anticoagulant effects of warfarin and other anticoagulant drugs.[22]

## Conclusion

Nonsteroidal anti-inflammatory drugs are a widely used class of drugs. Nurse anesthetists frequently encounter patients receiving these drugs and in many cases administer NSAIDs. Although these drugs provide numerous

benefits, they are not without risk. Their inhibition of physiologic processes such as prostaglandin, prostacyclin, and thromboxane formation results in varied effects. As a result, they possess a potential to interact with many commonly administered drugs, resulting in side effects. These risks, such as increased bleeding, decreased effects of antihypertensive medicines, or decreased renal elimination of other drugs, are of particular concern to the nurse anesthetist.

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## DISCLOSURES

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