NSAIDs and COX-2 Inhibitors
Raymond S. Sinatra, MD, Ph.D

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a large and varied class of peripherally acting analgesics that are among the most widely used pain medications worldwide. The class is well known to patients and surgeons alike, with over 70 million prescription-strength doses written every year and a large number of over-the-counter formulations readily available for use.\(^1,2\)

In the perioperative setting, NSAIDs play a key role in multimodal analgesia, and are prescribed as alternatives or adjuncts to opioid-based analgesia. NSAIDs possess analgesic and anti-inflammatory, as well as antipyretic, properties and have proven efficacy in the treatment of headache, osteoarthritis, and postoperative pain. In addition to oral tablets and transdermal preparations, two intravenously administered NSAIDs, ketorolac (Toradol) and ibuprofen (Caldolor), have been approved for surgical pain management in the United States.\(^3,4\)

Site and Mechanism of Activity

The primary mechanism by which NSAIDs exert their analgesic effects is by inhibition of arachidonic acid–cyclooxygenase (COX) pathways.\(^1,2,5,7,7\) Two distinct pathways mediated by cyclooxygenase isoforms, COX-1 and COX-2, have been identified.\(^5,6\) Cyclooxygenase-1 is the normally expressed, homeostatic isoform that promotes platelet aggregation, renal blood flow, and gastric protection. In contrast, COX-2 is minimally expressed in normal settings but is markedly upregulated following trauma or surgery\(^5\) (Figure 8.1). Following tissue injury, arachidonic acid is released from damaged cell membranes and converted by COX-2 into prostaglandin E2 (PGE\(_2\)). PGE\(_2\) plays a critical role in nociceptor activation and initiation of the inflammatory cascade.\(^1,2,5,7\)

By inhibiting COX-2 and reducing PGE\(_2\) synthesis, NSAIDs decrease inflammatory hyperalgesia and allodynia (pain associated with innocuous stimulation).\(^1,5\) NSAIDs also block the recruitment of leukocytes and monocytes, and production of cytokines and other leukocyte-derived inflammatory mediators.\(^1,2,6,7\) Some NSAIDs are able to cross the blood-brain barrier, where they limit PGE\(_2\) synthesis in sensitized neurons and glial cells.\(^8\) In this manner, NSAIDs reduce local inflammation and can prevent both peripheral and central sensitization.

No analgesic class is without adverse effects, and NSAIDs are no exception. Common adverse effects of nonselective NSAIDs are related to their inhibition of homeostatic prostaglandins, and the resulting increase in risks of GI bleeding, platelet dysfunction, and renal failure.\(^1,5,9\) NSAIDS are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery, and caution is required in patients with a variety of common conditions, including asthma, hypertension, renal insufficiency, preexisting ulcer disease, and congestive heart failure, among others.\(^1,2,9,10\)

Prior to administration, clinicians must weigh potential advantages of NSAIDs, including reductions in opioid dose, vs their impact on surgical hemostasis and other aspects of patient safety. Not all NSAIDs are alike, therefore, agent-specific toxicity, black box warnings, COX-1 specificity, cost, and route of administration must also be considered.\(^1,10,11\)

Injectable Ketorolac

Ketorolac tromethamine (Toradol) was the first injectable NSAID approved for use by the FDA, and has been widely prescribed for surgical pain management for over 20 years. It is indicated for the short-term (≤5 days) management of moderate to moderately severe postoperative pain.\(^3\) A number of studies have evaluated the efficacy of IV ketorolac in postsurgical settings, noting significant reductions in pain, opioid-sparing effects, and facilitation
of recovery.\textsuperscript{12-14} Ketorolac administered alone in doses of 30 mg to 60 mg is as potent as 10 mg of morphine and is particularly useful in managing surgical and posttraumatic musculoskeletal pain and visceral pain.\textsuperscript{14} When employed as a multimodal analgesic, a 30-g loading dose of ketorolac, followed by 15-mg to 30-mg doses every 6 hours, provide useful augmentation of opioid-based analgesia or neural blockade.\textsuperscript{1,2} Unlike opioids, it is not associated with excessive sedation, cognitive dysfunction, or respiratory depression.

In contrast to many other NSAIDs, ketorolac is an extreme outlier in terms of its inhibitory effect on COX-1 relative to COX-2\textsuperscript{5} (Figure 8.2). This finding has important safety-related implications for perioperative use, since the negative effect of NSAIDs on renal function, GI mucosal integrity, and platelet function are the direct result of COX-1 inhibition.\textsuperscript{1,2,5,15} Platelet dysfunction associated with ketorolac can increase the risk for postoperative hematomas, wound site bleeding, and life-threatening occult bleeding.\textsuperscript{5,10} For this reason ketorolac has been withdrawn from the European market. In the United States, IV ketorolac is contraindicated in patients with or who have a history of GI bleeding or those at risk for major postsurgical bleeding. As such, the prescribing information for IV ketorolac contains a black box warning against its use as a prophylactic analgesic prior to any form of major surgery.\textsuperscript{3} In an effort to reduce dose-dependent COX-1 interactions, we recommend that postoperative doses of ketorolac be reduced to 7.5 mg to 10 mg every 6 hours and given for no longer than 48 hours as part of a multimodal approach to surgical pain.

**Ibuprofen Injection (Caldolor)**

An injectable formulation of ibuprofen (Caldolor) was approved for use in the United States in June 2009, and it is indicated for management of mild to moderate pain by itself, and for management of moderate to severe pain as an adjunct to opioid analgesics.\textsuperscript{4} Similar to oral ibuprofen, the IV formulation inhibits both COX-1 and COX-2. When compared with IV ketorolac, however, the ibuprofen injection has a more “balanced” affinity for the COX isoenzymes (Figure 8.2). Lower selectivity for COX-1 may translate into reduced risk of platelet dysfunction and GI ulceration.\textsuperscript{4,10,11,15}

Recommended dosing guidelines for ibuprofen injection are 800 mg every 6 hours, with a maximum 24-hour dose of 3200 mg. Elderly and low weight patients (>50 kg) may experience effective pain control with 400-mg doses. The drug is supplied in vials containing either 400 mg or 800 mg of ibuprofen in 4 mL to 8 mL of clear solution. Unlike ketorolac, the drug should never be given as a rapid IV bolus. Instead, the contents of each vial should be diluted in 250-mL bags of sterile saline or lactated ringers, and infused over a period of 7 to 15 minutes.\textsuperscript{4} By following these dosing recommendations, maximal plasma concentrations ($C_{\text{max}}$) achieved with the 800-mg ibuprofen injection are double that observed with 800 mg of oral ibuprofen, and time to $C_{\text{max}}$ is considerably more rapid. These pharmacokinetic differences increase drug concentrations at the site of tissue injury and underscore rapid onset and high analgesic efficacy of the ibuprofen injection.

In a randomized double-blind, placebo-controlled trial, the safety and efficacy of ibuprofen injection was evaluated in 319 patients undergoing abdominal hysterectomy.\textsuperscript{16} Injectable ibuprofen 800 mg given at wound closure and every 6 hours for up to 5 days was associated with significant reductions in pain with movement (14% reduction at 24 hours vs placebo; $P=0.010$) and a 19% reduction in 24-hour morphine requirements ($P \leq 0.001$). When compared with patients treated with placebo, there was no difference in treatment-emergent adverse events, including wound site bleeding, reduced hematocrit, and renal toxicity.

Singla and colleagues evaluated the safety and efficacy of an ibuprofen injection administered preemptively as a multimodal analgesic.\textsuperscript{17} One hundred and eighty five patients undergoing major orthopedic surgery received either 800 mg IV ibuprofen or placebo prior to surgical incision, then every 6 hours for up to 5 days following surgery. Patients receiving ibuprofen injection required 31% less PCA morphine over the first 24 hours ($P \leq 0.001$). They also experienced reductions in pain at rest (32% vs placebo; $P < 0.001$) and with movement (26% vs placebo; $P < 0.001$) (Figure 8.3). These data indicate that ibuprofen injection offers greater analgesic efficacy when administered preemptively. Preincisional administration did not reduce overall patient safety, as there were no differences in surgical bleeding, renal toxicity, or other adverse events between the study groups.

Ibuprofen injections are well tolerated by high-risk patients. No renal, GI, or hemostatic abnormalities were noted in debilitated burn injured patients receiving multiple doses of ibuprofen injection for control of fever.\textsuperscript{4} Like other NSAIDs, ibuprofen injection should be withheld in patients with active GI ulcers, prerenal azotemia, patients with anticipated or ongoing surgical site bleeding, and patients recovering from CABG surgery.\textsuperscript{4}

**COX-2 Inhibitors**
Research and development of the COX-2 inhibitors was driven by the need to improve GI safety while maintaining analgesic efficacy.\textsuperscript{1,5,11} In this regard, 60% of patients taking nonselective NSAIDs report GI tract adverse effects. COX-2 inhibitors, or coxibs, are a subclass of NSAIDs that are relatively more specific for the COX-2 enzyme isoform compared with COX-1. Selective inhibition of the COX-2 provides powerful anti-inflammatory and anti-nociceptive effects without compromising the constitutive benefits of COX-1.\textsuperscript{1,5,10,11} Following long-term coxib administration, the incidence of gastric ulcer is similar to that observed with placebo, and significantly lower than that observed with nonselective NSAIDs.\textsuperscript{5,10} Despite this increase in safety, the COX-2 inhibitors should not be given to patients with active bleeding ulcers. Current guidelines suggest pairing a COX-2 inhibitor with a proton pump inhibitor in patients with a prior history of GI bleeding.\textsuperscript{1,2} An additional clinical benefit of coxibs is that they have no effect on platelet function. They do not prolong the bleeding time and do not increase risks of wound site or occult bleeding.\textsuperscript{1,5,10,11}

The first COX-2 inhibitor approved by the FDA in 1998 was celecoxib (Celebrex). Following the withdrawal of rofecoxib (Vioxx) and valdecoxib (Bextra), celecoxib is the only COX-2 inhibitor currently available for acute pain management. The analgesic effectiveness of oral celecoxib has been confirmed and its hemostatic safety demonstrated in several surgical models.\textsuperscript{1,2,11,18} Gimbel and colleagues\textsuperscript{18} reported that celecoxib 200 mg provided a similar onset and overall quality of analgesia as that observed with hydrocodone 10 mg/acetaminophen 1000 mg in patients recovering from orthopedic surgery. Celecoxib was not associated with increased blood loss, and patients benefited from a lower incidence of GI adverse events.

Celecoxib is well suited for preemptive or preincisional dosing as it is not associated with impaired platelet function or prolongation of the bleeding time. Recommended dosing is 200 mg to 400 mg oral celecoxib with a small sip of water given 2 hours prior to induction of anesthesia. Thereafter depending on patient age, weight, and comorbidity, doses of 100 mg to 200 mg can be administered every 12 hours for 5 days or longer.\textsuperscript{19}

The FDA has mandated a black-box warning for celecoxib with regard to risks of cardiovascular and cerebrovascular thrombosis with long-term use.\textsuperscript{19} Because of these risks, administration of celecoxib fell out of favor for several years. More recently, the efficacy and short-term safety benefits of celecoxib have been reconsidered by surgeons and anesthesiologists who are increasingly utilizing the drug for perioperative pain management.\textsuperscript{1,2,10} To minimize cardiovascular complications, do not administer celecoxib in CABG surgery, or in patients at high risk for cardiovascular and cerebrovascular thromboses.\textsuperscript{19} Since COX-2 also has renal protective effect and controls renin release in hypovolemic patients, celecoxib (as well as NSAIDs) is also contraindicated in prerenal azotemia.\textsuperscript{19}

### Optimizing NSAIDs Benefits While Reducing Risks

One criticism of analgesic regimens that employ NSAIDs or COX-2 selective inhibitors has been an inability to consistently correlate reductions in opioid consumption and improved pain control with measurable improvements in clinical outcomes and patient functionality.\textsuperscript{1,2,10,11} Most trials have been underpowered, single-dose, short-term evaluations that could not reliably discern significant differences between treatment groups.\textsuperscript{1,2} Clinical advantages have been detected when the results of many similar trials are pooled together. Marret and coworkers\textsuperscript{20} published a meta-analysis of 22 randomized, double-blind studies that included 2307 postsurgical patients using IV PCA morphine who were either treated or not treated with NSAIDs. Coadministration of NSAIDs significantly reduced the incidence of postoperative nausea and vomiting by 30%, nausea alone by 12%, vomiting alone by 32%, and sedation by 29%. NSAIDs had no effect on pruritus, urinary retention, and respiratory depression. A regression analysis indicated that reductions in morphine consumption correlated positively with reductions in the incidence of nausea and vomiting (Figure 8.4). In a separate analysis of 52 randomized placebo-controlled trials, Elia and colleagues\textsuperscript{21} compared postsurgical NSAIDs and coxib based multimodal analgesia vs opioid monotherapy. Coadministration of NSAIDs was associated with a 15% to 55% decrease in opioid dose requirements, reductions in pain intensity at 24 hours, and a reduced incidence of nausea/vomiting (from 29% to 22%) and sedation (from 15.4% to 12.7%).

During movement and ambulation, increased tension at the incision site exacerbates tissue injury resulting in a heightened inflammatory response and further sensitization of peripheral nociceptors. NSAIDs can attenuate this response as evidenced by studies in which patients treated with either injectable ibuprofen\textsuperscript{17} or rofecoxib\textsuperscript{22} reported significant reductions in incident pain associated with movement. Buvanendran and colleagues\textsuperscript{22} utilized a protocol designed to detect improvements in patient functionality following total knee arthroplasty surgery. Patients treated with perioperative doses of a COX-2–selective inhibitor reported improved relief of incident pain and benefited from significant increases in angle of knee flexion during rehabilitation. A well-powered clinical trial evaluating recovery from abdominal gynecological surgery found that patients randomized to receive multiple perioperative doses of COX-2–selective inhibitors not only reported lower pain intensity scores and required significantly less...
PCA morphine, but also benefited from lower sedation scores and more rapid return of bowel function.\textsuperscript{23} The common denominator that reduced incident pain and facilitated return of bowel function in these trials was the fact that coxibs and NSAIDs were utilized in a well-defined multimodal treatment plan, the first dose was given prior to rather than following surgery, and follow-up doses were given for extended periods of time (5 days).\textsuperscript{17,22,23}

Despite the clear analgesic advantages offered by NSAIDs and coxibs, a large number of surgeons either withhold or limit dosing in perioperative settings. Many surgeons routinely discontinue NSAIDs 5 to 10 days prior to surgery, citing risks of increased perioperative bleeding and possible inhibition of wound healing.\textsuperscript{1,2} The withdrawal of NSAIDs prior to relatively noninvasive or low blood loss procedures is unnecessary in most patients. Moreover, abrupt discontinuance of NSAIDs may increase preoperative discomfort and ensures that surgery is performed in a setting of increased inflammation and sensitization. If caregivers are truly concerned about potential increases in surgical bleeding, preoperative patient comfort and postsurgical safety can be maintained by discontinuing nonselective NSAIDs 3 to 5 days prior to surgery and substituting the COX-2 inhibitor celecoxib.

There is no evidence to suggest that a short-term administration of NSAIDs (24 to 36 hours) has negative effects on orthopedic surgical outcomes. Nevertheless, some orthopedic surgeons avoid NSAIDs following total joint replacement procedures as well as spinal fusion surgery, fearing that inhibition of the inflammatory response may impair bone regrowth and increase the risk of fusion or prosthetic failure. Fusion failure was reported in one retrospective trial where relatively high doses of ketorolac were administered for prolonged periods of time.\textsuperscript{24} We recommend that caregivers follow guidelines promoted by the American Society of Anesthesiology.\textsuperscript{25} Unless contraindicated, NSAIDs should always be considered for postsurgical pain management, with the lowest effective dose utilized for the most appropriate duration of therapy. NSAID and coxib pharmacology and dosing guidelines are presented in Table 8.1.

**Conclusion**

Perioperative administration of injectable NSAIDs or celecoxib can attenuate peripheral inflammation and nociceptor sensitization, and should be considered key analgesic components for the multimodal management of postsurgical pain. Parenteral NSAIDs offer rapid analgesic onset and utility in patients who cannot take oral medications. A more favorable COX-1 vs COX-2 selectivity ratio, lack of restriction to preoperative dosing, and up to 5-day dosing interval are suggestive that ibuprofen injection may offer clinical safety advantages over IV ketorolac. Several new NSAID formulations, including injectable diclofenac and intranasal ketorolac, are awaiting FDA approval for use in the United States, and offer additional dosing options and versatility in postsurgical settings, as well as potential improvements in safety.

**REFERENCES**


TABLE 8.1 — NSAIDs Approved for Surgical Pain Management

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
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\(^a\) Per package inserts.
\(^b\) Blackbox warning.

FIGURE 8.1 — Mechanism of Action of NSAIDs and Coxibs

Two forms of cyclooxygenase, COX-1 and COX-2, have been identified. COX-1 is primarily responsible for the synthesis of constitutive or protective PGEs, which mediate the normal function of platelets, the kidneys, and the GI tract. The COX-2 isoform is induced following tissue injury and is primarily responsible for the synthesis of PGEs that initiate and maintain pain and inflammation. By inhibiting COX-1, NSAIDs diminish levels of PGE, which may result in GI ulceration, impaired wound site hemostasis, and renal dysfunction. The analgesic effects of NSAIDs are related to their inhibition of COX-2 and subsequent reduction in PGEs that cause pain inflammation and fever. Studies of selective COX-2 inhibitors have revealed an enhanced risk for CV events.


FIGURE 8.2 — Inhibition of COX-2 Relative to COX-1

Currently, there are two injectable NSAIDs available for use in the United States: ibuprofen injection (Caldolor) and ketorolac (Toradol). While both are nonselective NSAIDs, they differ in their degree of inhibition of COX-2 relative to COX-1. Ibuprofen inhibits COX-1 2.5 times more than COX-2, whereas ketorolac inhibits COX-1 >300 times more than COX-2.


FIGURE 8.3 — Pain Assessed With Movement

Patients treated with presurgical ibuprofen injection (800 mg), followed by repeated doses every 6 hours, awoke in less pain and remained in less pain throughout the postoperative period. Patients experienced a 26% reduction in pain intensity scores when pain was assessed with movement.

\(^a\) Statistical significance was demonstrated at each assessment point.


FIGURE 8.4 — Coadministration of NSAIDs Reduces Postoperative Opioid Adverse Events

A regression analysis of nausea and vomiting from 22 postsurgical trials in which patients utilized IV-PCA morphine and were either treated or not treated with NSAIDs. Reductions in the incidence of nausea and vomiting correlated positively with reductions in morphine consumption.