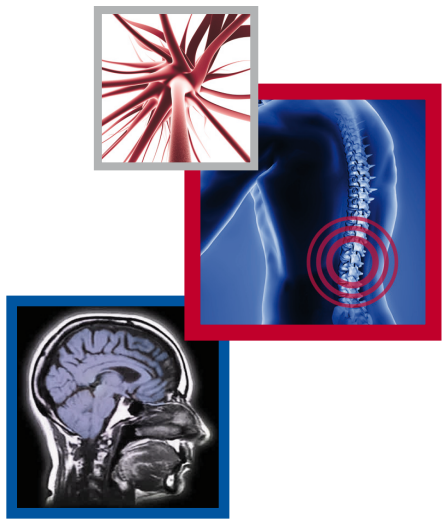
REVIEW

Intravenous ibuprofen for postoperative pain



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Practice Points

- Intravenous (iv.) ibuprofen is a key addition to the perioperative pain management regimen in any surgical setting.
- iv. ibuprofen is available for preoperative administration, differentiating itself from iv. ketorolac, which is contraindicated for preoperative use.
- iv. ibuprofen has a more favorable COX-1:COX-2 inhibition ratio than iv. ketorolac, leading to potentially less renal, gastrointestinal and bleeding side effects.
- From ambulatory exploratory surgery to in-patient colon resection surgery, patients treated pre-, intra- and post-operatively with iv. ibuprofen will have reduced narcotic analgesic requirements and lower pain levels with an excellent safety profile.
- Surgical patients treated with iv. ibuprofen may recover faster, due to the direct analgesic and anti-inflammatory effects combined with reduced opioid requirements and therefore reduced opioid-related side effects.
- Shortened iv. ibuprofen infusion data are available, showing a robust C_{max} and the possibility for potentiation of the analgesic effect.
- iv. ibuprofen may have additional synergistic multimodal analgesia effects when used in combination with central and peripheral nerve blocks.
- Analgesic utility of iv. ibuprofen extends beyond surgical pain, as there are clear benefits of the product in:
  - The emergency department for musculoskeletal injuries and migraine headache
  - The hospital floor for general pain management
  - Out-patient surgery centers to speed discharge and limit narcotic use

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SUMMARY A multimodal analgesic approach involving intravenous NSAIDs in the perioperative setting has been common practice for many years outside of the USA. As an adjunct to the central analgesic effects of opioids, intravenous NSAIDs may be important for perioperative pain management due to their analgesic and peripheral anti-inflammatory effects. Together, these agents may attenuate the pain resulting from the surgical procedure better than either agent used singly. Prior to 2009, ketorolac was the only intravenous NSAID approved in the USA for the treatment of pain. However, in June 2009, intravenous ibuprofen (Caldolor®) was approved by the US FDA for the treatment of mild-to-moderate pain as a single agent and moderate-to-severe pain as an adjunct to opioids. A growing body of research has demonstrated the efficacy and safety of intravenous ibuprofen in the perioperative setting and is reviewed herein.

Background

NSAIDs, in one form or another, have been used for centuries for the treatment of pain and fever and to this day are the most frequently prescribed and utilized medications in the world [1]. One particular NSAID, ibuprofen – (*RS*)-2-(4-[2-methylpropyl]phenyl)propanoic acid – has been used for more than 40 years in its oral form **(Figure 1)** [2]. Recently, an intravenous (iv.) formulation of ibuprofen (Caldolor®, Cumberland Pharmaceuticals, Inc., TN, USA) was approved by the US FDA for the treatment of pain and reduction of fever in adult patients [3,4].

COX enzyme isoforms 1, 2 and 3 are found throughout the body and play a critical role in the physiological transduction of pain, inflammation and fever, as well as a myriad of other physiological roles including coagulation and chemoprotection of the gastrointestinal (GI) mucosa [5]. COX-1 is expressed in platelets and the GI mucosa, while COX-2 is found throughout skeletal, smooth and cardiac muscle [5]. Very little is understood about COX-3 at this time, but it appears to be expressed only in the brain [6]. For the most part, NSAIDs exact their desired clinical effects through inhibition of COX-2, while inhibition of COX-1 may result in complications such as bleeding or adverse GI effects [5]. These differences in COX isoform expression spurred the development of COX-2-specific inhibitors, some of which were removed from the market due to cardiac safety issues associated with higher doses [7].

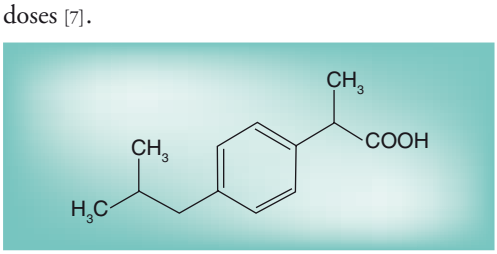

Figure 1. Ibuprofen.

Ibuprofen is considered a nonspecific inhibitor of COX enzymes with a COX-1 to COX-2 inhibition ratio of approximately 2.5:1 [8]. However, other NSAIDs such as ketorolac have a COX-1 to COX-2 inhibition ratio of approximately 330:1, which may explain the bleeding and GI risks listed in the product labeling for ketorolac [8,9]. The analgesic effect of ibuprofen results from a combination of its central analgesic effect, which is poorly understood, and its anti-inflammatory effect, which results from inhibition of COX-2 in the periphery, particularly in skeletal muscle [10–12]. When used in conjunction with centrally acting analgesics such as opioids, the analgesic and peripheral anti-inflammatory effects of ibuprofen provide a powerful type of synergy to further improve pain relief greater than either drug given alone and can also reduce drug-related side effects [13]. This approach is a type of multimodal analgesia [13].

It is well established that during surgery both peripheral and central sensitization is provoked by the surgical incision and this hypersensitivity leads to pain postoperatively [14]. Studies assessing the timing of these effects found that routine tissue injury during surgery can lead to a particularly prolonged state of increased central excitability and therefore pain [14]. This led Woolf and Chong to first postulate in 1993 that the key to treating postoperative pain would be preoperative analgesic dosing in conjunction with intra- and post-operative dosing to prevent the establishment of central sensitization [14]. Woolf and Chong proposed to pre-empt pain by beginning analgesic treatment in advance of pain instead of waiting for pain to present and then treating it [14]. A recent review article has summarized almost 20 years of pre-emptive analgesia research and the authors found that the data are largely in support of Woolf and Chong's theory, although some studies did not demonstrate a significant difference in pain scores or opioid requirements

when comparing preoperative and postoperative dosing [15].

Until the approval of iv. ibuprofen in 2009, the only other iv. NSAID approved in the USA was ketorolac, which is specifically contraindicated for use prior to surgery [3,9]. The main concern with the use of ketorolac in the perioperative setting is an increased risk of bleeding, although use of ketorolac in the perioperative period has been reported [9,16]. Perioperative ketorolac may also increase the risk of renal dysfunction during and after surgery [9,16]. iv. ibuprofen has no such contraindication and has been specifically studied for pre-emptive use. A clinical study in orthopedic surgeries demonstrated the benefits of combined pre- and post-operative dosing of iv. ibuprofen resulting in greater reductions in postoperative pain scores and morphine requirements, supporting Woolf and Chong's theory [17].

Indications & usage

iv. ibuprofen is indicated for the management of mild-to-moderate pain and as an adjunct to opioid analgesics for moderate-to-severe pain in adult patients [3]. While this article focuses on postsurgical pain, iv. ibuprofen may be used to treat any pain including headaches, musculoskeletal aches/injuries, burns or any other painful condition [3]. iv. ibuprofen is also indicated for the reduction of fever in adult patients [3]. Pivotal studies in pediatric patients are currently underway for both the pain and fever indications [101,102].

Dosage & administration

For the treatment of pain, the recommended dose is 400–800 mg iv. ibuprofen every 6 h, as necessary [3]. The total daily dose limit is 3200 mg [3]. The product labeling mandates an infusion time of no less than 30 minutes for iv. ibuprofen [3]. However, a more rapid 5–7 minute infusion of iv. ibuprofen has been successfully studied in healthy volunteers and is currently being utilized in a number of clinical studies [18].

Clinical pharmacology

Mechanism of action/pharmacodynamics

As an NSAID, iv. ibuprofen possesses analgesic, antipyretic and anti-inflammatory activity [3]. The analgesic and anti-inflammatory activity of iv. ibuprofen results from a combination of central and peripheral COX-2 inhibition, respectively [3,5,11,12,19]. The antipyretic effect of iv. ibuprofen results from inhibition of prostaglandin synthesis in the hypothalamus [3,10].

Pharmacokinetics

iv. ibuprofen is comprised of a racemic mixture of [-]R- and [+]S-isomers, with the [+]S-isomer being responsible for the activity of the drug and the [-]R-isomer serving as an inactive reservoir of the drug which is actively interconverted to the active [+]S-isomer [3,20]. iv. ibuprofen is highly bound to plasma proteins (>99% bound at 20 µg/ml) and can have a highly variable volume of distribution depending on the age and health of the patient [3]. The product labeling for iv. ibuprofen shows data from an unpublished study of a 60-min infusion of single doses of 400 and 800 mg iv. ibuprofen [3]. This study revealed comparable pharmacokinetic parameters to that of orally administered ibuprofen, with a $T_{½}$ of approximately 2 h and similar values for area under the curve (AUC), the C_{max} and the T_{max} [3,20]. In one of the pivotal fever trials, pharmacokinetic data were gathered for a 30-min infusion of 100, 200 and 400 mg iv. ibuprofen **(Table 1)** [21]. This study revealed a significantly higher C_{max} and faster T_{max} than previous studies of iv. ibuprofen, while $T_{½}$ remained approximately 2 h and AUC was unchanged **(Table 1)** [21]. As previously mentioned, a more recent healthy volunteer study assessed the pharmacokinetics of a 5–7-min infusion of 800 mg iv. ibuprofen compared with 800 mg oral ibuprofen and revealed a further increase in C_{max} and faster T_{max} than previous studies of iv. ibuprofen, with no added side effects **(Table 1)** [18].

Clinical evidence

Overview of clinical trials

Three adult surgical studies assessing the efficacy and safety of iv. ibuprofen for the treatment of postoperative pain have been completed so far [17,22,23]. While all three studies utilized a 30-min infusion of the drug, the time at which the first dose was given differed between the first two studies and the third study [17,22,23]. The first study was a multicenter, randomized, double-blind, placebo-controlled dose-ranging trial of iv. ibuprofen in the management of postoperative pain in patients undergoing elective single-site orthopedic or abdominal surgery [22]. The first dose of iv. ibuprofen (400 or 800 mg) or placebo was given at closure of the surgical wound and then dosing was continued every 6 h for the first 2 days with optional dosing out to day 5 [22]. The use of ibuprofen 800 mg iv. every 6 h was associated with a 22% reduction in median morphine use over the immediate 24 h following

Table 1. Intravenous ibuprofen pharmacokinetic parameters.

Parameter	30-min infusion (hospitalized patients)	5–7-min infusion (healthy volunteers)	
	iv. ibuprofen (400 mg)	iv. ibuprofen (800 mg)	Oral ibuprofen (800 mg)
Number of patients	31	12	12
AUC (µg/h/ml)	70.6 + 31.9	190.6 + 35.6	196.4 + 36.2
C_{max} (µ/ml)	39.8 + 17.8	120.3 + 13.5	62.8 + 12.4
T_{max} (h)	0.5 + 0.0	0.11 + 0.01	1.5 + 0.6
$T_{½}$ (h)	2.26 + 1.0	2.0 + 0.5	1.9 + 0.3

AUC: Area under the curve; iv.: Intravenous.

surgery, while ibuprofen 400 mg iv. every 6 h was associated with only a 3% reduction in median morphine use [22]. Pain at rest and pain with movement were also assessed in the study using a patient-completed visual analog scale (VAS), and the 800 mg dose of iv. ibuprofen showed significant reductions in pain at rest ($p = 0.001$) and with movement ($p = 0.002$) over the first 24 h compared with placebo, while the 400 mg dose of iv. ibuprofen significantly reduced pain with movement ($p = 0.021$) [22]. This study demonstrated the efficacy of iv. ibuprofen for the treatment of postoperative pain by reducing the opioid analgesic requirement while further improving postoperative pain scores. This study also established 800 mg iv. ibuprofen as the appropriate dose for future pain studies [22].

The second study was a multicenter, randomized, double-blind, placebo-controlled trial in women undergoing elective abdominal hysterectomy and was designed to confirm the results of the first study [23]. As in the first study, the first dose of iv. ibuprofen (800 mg) or placebo was given at closure of the surgical wound, and then dosing was continued every 6 h for the first 2 days. The study was also powered for morphine-sparing [23]. In this study, iv. ibuprofen demonstrated a significant 16% reduction ($p < 0.001$) in morphine use over the first 24 h when compared with placebo and also caused a significant reduction in pain at rest (21%; $p = 0.011$) and pain with movement (14%; $p = 0.010$) measured by VAS [23]. Patients treated with iv. ibuprofen also had a significantly faster time to ambulation than patients treated with placebo [23]. This study confirmed the efficacy of 800 mg iv. ibuprofen for the treatment of postoperative pain and demonstrated that patients receiving the drug may recover faster [23].

The third study was designed to assess whether preoperative dosing of iv. ibuprofen might further decrease postoperative pain by decreasing central sensitization [14]. This study was a multicenter, randomized, double-blind, placebo-controlled trial in postoperative orthopedic patients powered for pain reduction (measured by VAS), and iv. ibuprofen (800 mg) or placebo was administered at the induction of anesthesia (prior to surgery) and every 6 h (for up to 5 days) until the resolution of pain [17]. In this study, iv. ibuprofen-treated patients experienced significantly less pain at rest (32%; $p < 0.001$) and with movement (26%; $p < 0.001$) when compared with placebo in the immediate postoperative period (study hour 6–28) [17]. In addition, patients treated with iv. ibuprofen experienced significantly less pain upon waking up from surgery when compared with placebo (14%; $p = 0.012$), and iv. ibuprofen-treated patients also experienced a 31% reduction ($p < 0.001$) in morphine use compared with placebo-treated patients [17]. This study demonstrated the beneficial effects of preoperative administration of iv. ibuprofen by providing the most robust analgesic data to date for the drug and laid the groundwork for clinical use and future investigational work [17].

Adverse reactions

The safety and tolerability of iv. ibuprofen for the treatment of postoperative pain was assessed in the three aforementioned adult surgical pain studies [17,22,23]. Combined across these studies, 403 patients received 800 mg iv. ibuprofen, 134 patients received 400 mg iv. ibuprofen and 373 patients received placebo, with all patients having access to morphine [17,22,23] [Cumberland Pharmaceuticals, Inc., Data on File]. There was no statistical difference in the incidence of adverse events between the iv. ibuprofen and placebo treatment groups across these studies, as 350 adverse events were reported in the 403 patients who received 800 mg iv. ibuprofen (87%; $p = 0.380$ compared with

placebo), 118 adverse events were reported in the 134 patients who received 400 mg iv. ibuprofen (88%; p = 0.752 compared with placebo), and 332 adverse events were reported in the 373 patients who received placebo (89%) [17,22,23] [Cumberland Pharmaceuticals, Inc., Data on File]. Adverse events frequently reported by the patients treated with iv. ibuprofen (and placebo) in these studies included nausea, vomiting and constipation, all of which are consistent with the adverse effects typically seen in surgical patients administered general anesthesia and morphine analgesia [17,22,23] [Cumberland Pharmaceuticals, Inc., Data on File]. In some cases, the patients in the iv. ibuprofen treatment group experienced less of these side effects than patients in the placebo group, suggesting that the reduction in opioid requirements by iv. ibuprofen may reduce opioid-related side effects. However, since none of these differences reached statistical significance, it is difficult to conclude if any of the numerical differences between treatment groups are clinically significant.

The product labeling for iv. ibuprofen contains the US FDA required NSAID warnings and precautions for cardiovascular thrombotic events, GI effects such as inflammation and bleeding, renal and hepatic injury, hypertension, congestive heart failure, serious skin reactions and bleeding. However, these precautions are based on years of experience with various NSAIDs associated with long-term treatment, and none of the adult surgical studies utilizing short-term dosing noted any differences between treatment groups in the incidence of GI-, renal-, hepatic-, cardiovascular-, respiratory- or bleeding-related serious adverse events. It is also important to keep in mind that clinical trials are conducted under widely varying conditions and therefore adverse reaction rates observed in the clinical trials of iv. ibuprofen cannot be compared directly with the rates in the clinical trials of other oral and iv. NSAIDs, and may not reflect the rates observed in standard of care practice.

Drug interactions

iv. ibuprofen has possible drug–drug interactions with aspirin, anticoagulants, ACE inhibitors, diuretics, lithium and methotrexate [3]. These drug–drug interaction data result from the large amount of experimental, clinical trial, observational and anecdotal evidence gathered over more than 40 years of oral ibuprofen use [2].

Aspirin

Coadministration of aspirin with ibuprofen may displace ibuprofen from plasma proteins, thereby raising the concentration of free ibuprofen in the bloodstream [3]. However, studies have demonstrated that this does not alter the clearance of ibuprofen and the clinical significance, if any, remains unknown [3]. Concomitant administration of multiple NSAIDs is typically not recommended due to the potential for increased side effects [3].

Anticoagulants

Anticoagulants such as warfarin may potentiate GI bleeding associated with NSAID use, and coadministration of warfarin and an NSAID together puts patients at a higher risk for serious GI bleeding than when each drug is used singly [3]. However, clinical studies of iv. ibuprofen allowed partial anticoagulant therapy, including warfarin, and no increase in GI or general bleeding events was noted [17,22,23].

ACE inhibitors

The antihypertensive effect of ACE inhibitors such as ramipril and lisinopril may be decreased by coadministration of an NSAID such as iv. ibuprofen [3].

Diuretics

The natriuretic effects of diuretics such as furosemide and thiazides have been shown to be reduced in some patients who were already taking ibuprofen [3]. This interaction is believed to occur due to ibuprofen-mediated inhibition of renal prostaglandin production [3].

Lithium

NSAIDs such as ibuprofen have been demonstrated to reduce renal lithium clearance and thereby elevate plasma lithium levels, possibly resulting in lithium toxicity [3]. Ibuprofen-mediated inhibition of renal prostaglandin synthesis is thought to be the mechanism of action behind this interaction, as well [3].

Methotrexate

Small animal studies have shown that NSAIDs can decrease the renal elimination of methotrexate by reducing tubular secretion of the drug, resulting in liver, kidney and lung toxicity [3].

iv. ibuprofen also lists a possible interaction with H_2 antagonists (ranitidine and cimetidine), but clinical evidence of this interaction is

lacking [3]. The clinical trials involving iv. ibuprofen did not discover any drug–drug interactions; however, the studies were not designed to include any prospective assessments of altered drug metabolism, drug transport or plasma protein binding.

Use in specific populations

Pregnancy

In terms of possible teratogenic effects, iv. ibuprofen is a pregnancy category C medication prior to 30 weeks gestation and a Pregnancy Category D medication starting at 30 weeks gestation [3]. A pregnancy category C designation means that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate, well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. A pregnancy category D designation means there is definitive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits still may warrant use of the drug in pregnant women despite potential risks. These precautions and many others are based on the many years of experimental and clinical use of oral ibuprofen.

Labor & delivery

The effects of iv. ibuprofen on labor and delivery in pregnant women are unknown, but animal studies have shown that maternal exposure to NSAIDs and other inhibitors of prostaglandin synthesis increased the incidence of dystocia and delayed parturition and decreased offspring survival [3,24].

Nursing mothers

No studies have been completed to determine whether iv. ibuprofen is excreted in human milk, but due to the potential of serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug [3]. However, studies with oral ibuprofen suggest that only a very small amount of the drug enters the breast milk and therefore poses little, if any, risk to the nursing infant [25].

Pediatric use

The safety and efficacy of iv. ibuprofen for the management of pain and reduction of fever has not been established in pediatric patients under the age of 17 years [3]. However, pediatric studies of iv. ibuprofen for pain and fever indications are currently underway.

Geriatric use

Clinical studies of iv. ibuprofen do not involve a sufficient number of subjects aged 65 years and over to determine whether the elderly respond differently from younger patients [3]. Elderly patients have a greater frequency of decreased hepatic, renal and cardiac function, as well as a greater incidence of concomitant diseases and medications and serious GI adverse events. Therefore, dose selection of iv. ibuprofen for elderly patients should be cautious [3]. A study of a different formulation of iv. ibuprofen involved 455 hospitalized patients with septic shock with an average age of 55 years [26]. In this study, 800 mg iv. ibuprofen was administered every 6 h for 48 h consecutively and no increased incidence of renal dysfunction, GI bleeding or other adverse events was noted [26].

Severity of illness

Although not discussed in the iv. ibuprofen product labeling, one of the pivotal fever studies found a significant difference in the pharmacokinetics of iv. ibuprofen in hospitalized patients when stratified by their severity of illness ('critically ill' defined as those on mechanical ventilation or vasopressor support vs noncritically ill) [21]. The study found that ibuprofen concentrations were lower at the same times and doses in the critically ill patients compared with the noncritically ill patients, and that these data correlated with decreased antipyretic efficacy in the critically ill patients [21]. The critically ill patients in this study may have had a larger volume of distribution, leading to lower blood levels of the drug [27].

Future perspective

The prevention and management of postoperative pain remains an ever-evolving field. A multimodal analgesic approach, particularly one that minimizes or eliminates opioids, will likely dominate postoperative pain management for years to come. iv. NSAIDs such as iv. ibuprofen will also play a greater role in the management of postoperative pain due to their ability to treat the inflammatory pain caused by surgical procedures. One growing area of interest involves adding regional anesthesia, such as nerve blocks, to a multimodal analgesic approach. Small studies and empirical findings suggest that these approaches may be able to eliminate the need for

opioids completely, but large prospective studies are needed to truly demonstrate this effect.

In addition, as society focuses on reducing healthcare costs, future studies will assess whether nonopioid analgesics such as iv. ibuprofen may help patients in the postoperative setting hasten their recovery and reduce their hospital stay, thereby reducing costs and their burden on the healthcare system.

Financial & competing interests disclosure

PB Kroll is an investigator in ongoing clinical trials sponsored by Cumberland Pharmaceuticals. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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- ▪▪ of considerable interest

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▪▪ **The package insert/product labeling for intravenous (iv.) ibuprofen is critical in detailing the indications/usage, dosage/administration, clinical pharmacology, drug interactions and use in specific populations. The package insert/product labeling for iv. ibuprofen also describes a key unpublished Phase I pharmacokinetic study.**

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▪ **All three of the surgical pain studies** [17,22,23] **utilized a 30-min infusion of iv. ibuprofen and this study established (in healthy volunteers) that iv. ibuprofen could be given as a rapid infusion over 5–7 min, laying the groundwork for a more rapid infusion of iv. ibuprofen (and the analgesic benefits of a higher C_{max}) in future studies on surgical patients.**

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