

An integrated safety analysis of intravenous ibuprofen (Caldolor®) in adults

Stephen R Southworth¹

Emily J Woodward²

Alex Peng²

Amy D Rock²

¹North Mississippi Sports Medicine and Orthopaedic Clinic, PLLC, Tupelo, MS, ²Department of Research and Development, Cumberland Pharmaceuticals Inc., Nashville, TN, USA

Abstract: Intravenous (IV) nonsteroidal anti-inflammatory drugs such as IV ibuprofen are increasingly used as a component of multimodal pain management in the inpatient and outpatient settings. The safety of IV ibuprofen as assessed in ten sponsored clinical studies is presented in this analysis. Overall, 1,752 adult patients have been included in safety and efficacy trials over 11 years; 1,220 of these patients have received IV ibuprofen and 532 received either placebo or comparator medication. The incidence of adverse events (AEs), serious AEs, and changes in vital signs and clinically significant laboratory parameters have been summarized and compared to patients receiving placebo or active comparator drug. Overall, IV ibuprofen has been well tolerated by hospitalized and outpatient patients when administered both prior to surgery and postoperatively as well as for nonsurgical pain or fever. The overall incidence of AEs is lower in patients receiving IV ibuprofen as compared to those receiving placebo in this integrated analysis. Specific analysis of hematological and renal effects showed no increased risk for patients receiving IV ibuprofen. A subset analysis of elderly patients suggests that no dose adjustment is needed in this higher risk population. This integrated safety analysis demonstrates that IV ibuprofen can be safely administered prior to surgery and continued in the postoperative period as a component of multimodal pain management.

Keywords: NSAID, surgical pain, fever, perioperative analgesia, critical care, multimodal pain management

Introduction

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with a well known and long history of use. Oral ibuprofen was approved in the USA over 40 years ago and has been a nonprescription drug for more than 30 years. IV ibuprofen (Caldolor®, Cumberland Pharmaceuticals Inc., Nashville, TN, USA) was first approved in 2009 for the management of mild to moderate pain, moderate to severe pain in conjunction with narcotics, and for the reduction of fever in adults.¹ It is the only IV NSAID approved for the treatment of fever in the USA. Since 2002, the safety and effectiveness of IV ibuprofen has been investigated in ten clinical studies, Phases II–IV, conducted under a corporate investigational new drug application (Table 1).

Two other IV NSAIDs are currently available in the US market, ketorolac tromethamine injection (“ketorolac”, Toradol, Pfizer Inc., New York, NY, USA) and diclofenac sodium injection (“diclofenac”, Dyloject™, Hospira Inc., Lake Forest, IL, USA). Ketorolac injection was approved in 1989 for the short-term management of moderately severe, acute pain requiring analgesia at the opioid level.² Ketorolac is contraindicated for use in excess of 5 days, for minor or chronic pain, and for use

Correspondence: Amy D Rock
Department of Research and
Development, Cumberland
Pharmaceuticals Inc., 2525 West End
Avenue, Suite 950, Nashville,
TN 37203, USA
Tel +1 615 255 0068
Fax +1 615 627 0630
Email arock@cumberlandpharma.com

in pediatric patients. Additional limitations on ketorolac administration include prohibitions against all preoperative use, in patients with active ulcers or who are otherwise at a high risk of bleeding, those with advanced renal impairment, and women who are nursing. Diclofenac sodium injection was approved in December 2014 for the management of mild to moderate pain or moderate to severe pain either alone or in combination with opiates.³ Diclofenac is only approved for use in adults and is contraindicated in patients with known moderate to severe renal insufficiency who may become volume depleted. Neither of these IV NSAIDs are indicated for the treatment of fever.

In general, NSAIDs have analgesic, anti-inflammatory, and antipyretic properties, and their use is associated with recognized gastrointestinal (GI) and cardiovascular (CV) risks which are generally believed to be derived from the relative level of cyclooxygenase 1 (COX1) or COX2 inhibition.^{4,5} All three IV NSAIDs mentioned above are considered nonselective in terms of their COX1 and COX2 inhibition because they are capable of inhibiting both isoforms. However, Warner et al extensively investigated the COX1 and COX2 inhibitory capacity of over 40 NSAIDs using two in vitro assays, and their results permit ranking of these NSAIDs in terms of COX1 preference – ketorolac > ibuprofen > diclofenac – where ketorolac is the most COX1 selective, diclofenac is weakly COX2 selective (fourfold), and ibuprofen is essentially balanced (nonspecific).⁶ These in vitro results suggest that ibuprofen may have a preferable safety profile over ketorolac in terms of GI complications and over diclofenac in terms of CV complications.⁷ This hypothesis is supported by the clinical literature which demonstrates that ketorolac can be as much as fivefold more gastrototoxic than other NSAIDs.⁸ A meta-analysis of 28 studies pooled the relative risk (RR) of GI complications following usage of individual NSAIDs and found that ibuprofen had one of the most favorable risk profiles (RR = 1.8) as compared to diclofenac at 3.3 and ketorolac at 11.5.⁹ Further meta-analysis demonstrated that ibuprofen also had one of the lowest risk ratios for CV events, whereas diclofenac conferred a high risk of CV complications.¹⁰ A retrospective chart analysis of 9,658 patients receiving inpatient NSAID therapy concluded that diclofenac and aspirin were the NSAIDs most commonly associated with the emergence of adverse events (AEs).¹¹

Until recently, limited data have been available on the use of IV ibuprofen in hospitalized patients. Additional Phase IV trials have been conducted following the approval of IV ibuprofen by the FDA in 2009. This review presents a cumulative analysis of the clinical safety data available

regarding the use of IV ibuprofen for the treatment of pain and fever in hospitalized adults.

Materials and methods

Study selection

The data in this cumulative safety analysis are derived from all published and unpublished, sponsored clinical studies investigating IV ibuprofen (Caldolor®, Cumberland Pharmaceuticals Inc.) for the treatment of fever and/or pain in adult patients (Table 1). Eight clinical trials have been published previously. All studies were conducted under an active investigational new drug application and approved by the sites' local independent ethics committees. All enrollees were at least 18 years of age, and written informed consent was obtained either directly from the participant or from his/her legally authorized representative.

Assessments

In each clinical trial, pain was assessed using a validated 10-point Visual Analog Scale (VAS),¹² and fever was defined as a core body temperature of 38°C (100.4°F) or above. Safety was assessed based on the frequency and severity of treatment-emergent AEs as well as changes in vital signs and laboratory parameters. Treatment-emergent AEs were defined as events that arose or worsened after the initiation of study drug. All AEs were standardized to Medical Dictionary for Regulatory Affairs (MedDRA) version 10.1 or higher preferred term and system organ class and subsequently summarized by treatment and age group. Abnormal laboratory values were summarized as either 1) AEs when deemed as such by the Investigator, 2) as population means over time, or 3) as markedly abnormal laboratory values. The ranges defining markedly abnormal are included with the discussion of each relevant laboratory parameter.

Vital signs were summarized descriptively by treatment group using both observed values and change from baseline values. Markedly abnormal vital signs (MAVS) were defined as measurements outside the following ranges. Systolic blood pressure was defined as either "high", ≥ 180 mmHg with a ≥ 20 mmHg increase from baseline, or "low", ≤ 90 mmHg with a ≥ 20 mmHg decrease relative to baseline. Markedly abnormal diastolic blood pressure was noted if it was ≥ 105 mmHg with a ≥ 20 mmHg increase from baseline. Markedly abnormal pulse rates were defined as either "high", ≥ 120 bpm (beats per minute) with a ≥ 15 bpm increase from baseline, or "low", ≤ 50 bpm with a ≥ 15 bpm decrease from baseline.

For all measures, baseline was defined as the last value obtained prior to the initiation of any study drug, and change

Table 1 Adult Phase II–IV studies comprising the safety database

Study	IV ibuprofen (N)	Comparator (N)	Design	Treatment(s)	IV ibuprofen infusion time (minutes)	Initiation of IV ibuprofen dosing relative to surgery	Description
Morris et al ¹³	92	28	MC, Rand, DB, PC, MD	<ul style="list-style-type: none"> • IV ibuprofen 100 mg, 200 mg, or 400 mg • Placebo 	30	NA	Efficacy, safety and pharmacokinetics in hospitalized, adult, febrile patients. Patients were stratified by severity of illness (critically ill vs not critically ill)
Krudson et al ¹⁴	30	30	SC, Rand, DB, PC, MD	<ul style="list-style-type: none"> • IV ibuprofen 400 mg • Placebo 	30	NA	Efficacy and safety in hospitalized, adult, febrile patients with malaria
Southworth et al ¹⁵	272	134	MC, Rand, DB, PC, MD	<ul style="list-style-type: none"> • IV ibuprofen 400 or 800 mg + morphine • Placebo + morphine 	30	Intraoperative	Dose ranging efficacy and safety in adult abdominal or orthopedic surgery patients
Kroll et al ¹⁶	166	153	MC, Rand, DB, PC, MD	<ul style="list-style-type: none"> • IV ibuprofen 800 mg + morphine • Placebo + morphine 	30	Intraoperative	Efficacy and safety in adult abdominal surgery patients
Singla et al ¹⁷	99	86	MC, Rand, DB, PC, MD	<ul style="list-style-type: none"> • IV ibuprofen 800 mg + morphine • Placebo + morphine 	30	Preoperative	Efficacy and safety in hospitalized, adult, orthopedic surgery patients
Promes et al ¹⁸	40	21	MC, Rand, DB, PC, MD	<ul style="list-style-type: none"> • Placebo + morphine • IV ibuprofen 800 mg • Placebo 	30	NA	Efficacy and safety in hospitalized, pediatric and adult burn patients for fever and pain
Bergese et al ¹⁹	150	0	MC, OL, SD/MD	<ul style="list-style-type: none"> • IV ibuprofen 400 mg (fever) • IV ibuprofen 800 mg (pain) • IV ibuprofen 800 mg 	5–10	Postoperative ^b	Safety of a shortened infusion time in hospitalized patients with pain or fever
Gan et al ²⁰	300	0	MC, OL, SD/MD	<ul style="list-style-type: none"> • IV ibuprofen 800 mg 	5–10	Preoperative	Pre- and postoperative safety of a shortened infusion time in surgery patients
NCT01650519 ^{a,21}	20	31	SC, Rand, DB, AC	<ul style="list-style-type: none"> • IV ibuprofen 800 mg • IV ketorolac 30 mg (15 mg in patients ≥65 years) 	5–10	Preoperative	Safety and efficacy in adult knee arthroscopy procedures
NCT01901393 ^{a,22}	51	49	MC, Rand, DB, AC	<ul style="list-style-type: none"> • IV ibuprofen 800 mg • IV ketorolac 30 mg (15 mg in patients ≥65 years) 	5–10	Preoperative	Safety and efficacy in adult knee arthroscopy procedures

Notes: ^aPer study protocol, only serious adverse events were collected in the safety database; ^ba subset of subjects received IV ibuprofen postoperatively for surgery-associated pain.

Abbreviations: DB, double blind; IV, intravenous; MC, multi-center; MD, multiple dose; OL, open label; PC, placebo controlled; Rand, randomized; SC, single-center; SD, single dose; NA, not applicable; AC, active control.

from baseline is defined as the value at the named assessment time minus the baseline value. The generic term “study drug” refers to either IV ibuprofen, placebo, or active comparator, and patients treated for pain had access to rescue narcotics regardless of treatment allocation (eg, morphine). No transformations or imputations were applied to any safety data for the purposes of this analysis. All subjects who received at least one dose of any study drug are included, and all subjects were analyzed according to the actual drug received.

Statistical analysis

An integrated safety database comprising data from the studies listed in Table 1 was created. Each analysis dataset in the safety database was generated by combining the study data tabulation model tagged datasets from each individual study and adding required variables programmatically for standardization. Variables that were added include any that would be needed to generate combined analyses (eg, “treatment emergent” flags added to the AE dataset). The safety database contains the following datasets: subject level, AEs, exposure, laboratory results, and vital signs. Descriptive statistics were used to summarize the populations and safety data from these ten studies. For the purposes of this analysis, descriptive statistics refers to the sample size (N), mean, median, standard deviation, minimum, and maximum for any group variable. SAS software package version 9.2 was used and all analyses were subjected to formal verification procedures for accuracy and consistency. Due to differences in study design and data collection, not all analyses include all studies. Exceptions are noted with each figure or table.

Results

Study characteristics

All ten, company-sponsored, Phase II–IV studies conducted with IV ibuprofen in adult patients were included in this analysis and comprise the clinical trial safety database for IV ibuprofen (Table 1). The studies were conducted between 2002 and 2014. There were eight controlled and two open-label designs. In the eight controlled studies, which were all randomized and double-blind, subjects received either IV ibuprofen (Caldolor®) or comparator – IV ketorolac or placebo. Of the eight controlled studies, five evaluated the benefit of IV ibuprofen to treat pain (surgical), two to relieve fever, and one for the treatment of pain and fever. Doses of IV ibuprofen ranged from 100 to 400 mg for the indication of fever and up to 800 mg for pain. In the two open-label, surveillance trials, all subjects received IV ibuprofen. One of these studies investigated IV ibuprofen for pain (surgical) and one for pain (any etiology) or fever. Doses of IV ibuprofen

were either 400 mg (fever) or 800 mg (pain) in these studies. Safety data in the form of serious AEs (SAEs) were available from all ten studies, whereas AE (nonserious) data were available from eight studies. Clinically significant laboratory parameters were collected in six studies. Safety sub-analyses were conducted based on the different administration conditions used in several of the studies. Four trials investigated a shortened infusion time for IV ibuprofen (ie, 5–10 vs 30 minutes);^{19–22} four studies allowed dosing prior to surgery.^{17,20–22}

Patient population: demographics, exposure, and indications

For the purposes of this analysis, the safety population consisted of 1,752 adults who received at least one dose of any study drug. IV ibuprofen was administered to 1,220 (69.6%) patients, 452 (25.8%) received placebo, and 80 (4.6%) received IV ketorolac as an active control. Of the 1,220 subjects that received IV ibuprofen, 173 were treated for fever and 1,087 were treated for pain, with 40 of these patients being treated for both indications. Reasons for pain were both nonsurgical (N=100) and surgical (N=987) (Figure 1). The etiologies of nonsurgical pain included, for example, abdominal, back, and burn and are summarized elsewhere.¹⁹ Surgeries were predominantly gynecological or orthopedic in nature, and the most common procedure was hysterectomy (36.4%, Table 2).

The mean age in years was similar between the treatment groups, 47 for patients receiving IV ibuprofen, 44 for placebo, and 46 in the active control group (Table 3). While the majority of the study population were between the ages of 18 and 65 years (89%) and female (67%), there were 187 who were 65 years or older (defined as “elderly”). Of those patients ≥65 years, 146 received IV ibuprofen, 34 received placebo, and 7 received IV ketorolac. Patient age was similarly distributed between all treatment groups (Figure 2).

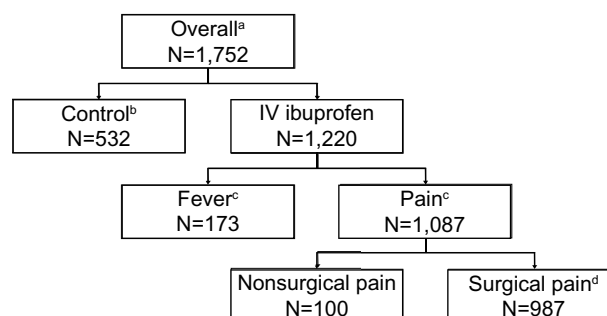


Figure 1 Disposition of patients.

Notes: ^aIncludes all adults, aged 18 years and older in Phase II–IV studies; ^bControl includes placebo and active comparator; ^cForty patients were treated for both pain and fever in Promes et al;¹⁸ ^dTypes of surgical procedures are summarized in Table 2.

Abbreviations: IV, intravenous; N, number.

Table 2 Types of surgical procedures in adult Phase II–IV studies

Category	Procedure	N	n
Obstetrical–gynecological		415	
	Hysterectomy		359
	Other OBGYN surgery		38
	Oophorectomy		13
	Laparoscopic ovarian tumor excision		5
Orthopedic		356	
	Knee ^a		139
	Knee ^b		74
	Hip ^a		69
	Other orthopedic		57
General		124	
	Shoulder ^a		17
	Hernia repair		47
	Other general surgeries		37
	Cholecystectomy		35
Urological		55	
	Breast mass excision		5
	Prostatectomy		24
	Cystectomy		22
	Other urological surgeries		9
Neurosurgical		20	
	Rhizotomy		10
	Spinal cord stimulator implant		10
Colorectal		12	
	Other colorectal surgeries		8
	Bowel surgery		4
Vascular		3	
Plastic surgery		1	
Otolaryngological		1	
Total		987	

Notes: ^aArthroplasty, replacement, or reconstruction; ^barthroscopy.

Abbreviations: N, total number in category; n, number of procedures; OBGYN, obstetrics and gynecology.

Table 3 Demographics

	IV ibuprofen (N=1,220)	Placebo (N=452)	Active control (N=80)
Age (years)			
Mean (SD)	47 (14.3)	44 (13.5)	46 (14.5)
Median	46	44	45
Min, Max	18, 92	18, 89	19, 77
Age category, N (%)			
18–64 years	1,074 (88)	418 (92)	73 (91)
≥65 years	146 (12)	34 (8)	7 (9)
Sex, N (%)			
Male	419 (34)	111 (25)	49 (61)
Female	801 (66)	341 (75)	31 (39)
Race, N (%)			
White	823 (67)	249 (55)	77 (96)
Black	250 (20)	133 (29)	2 (3)
Asian	106 (9)	56 (12)	0
Other	41 (3)	14 (3)	1 (1)
Weight (kg)			
Mean (SD)	83.6 (22.5)	82.5 (22.6)	88.5 (22.6)
Median	80.5	81.8	84.1
Min, Max	39.6, 198.0	35.1, 183.0	49.9, 161.4

Abbreviations: N, number; SD, standard deviation; Min, minimum; Max, maximum.

The average weight was also similar between the treatment groups (range: 82.5–88.5 kg).

On average, patients of either age stratum were treated with IV ibuprofen for 2 days with a maximum duration of 6 days (Table 4). The mean dose of IV ibuprofen received over the course of treatment was 2,860 mg, and the maximum received was 16,000 mg. The distribution of the most common, average, cumulative amount of IV ibuprofen received was biphasic with the highest proportions of patients receiving either 400–1,200 mg or 2,400–4,800 mg (37% each) during their hospitalization. Adults aged 18–64 years and elderly patients received similar amounts of IV ibuprofen for a similar duration.

Overall, 68% of patients received more than one dose of IV ibuprofen during their hospitalization, with five doses being the most common and 20 doses being the maximum (Table 4). The majority of patients were on an 800 mg regimen (78%).

Safety analyses

Most frequent AEs in the overall adult population

Ten Phase II–IV clinical studies of IV ibuprofen have been completed, eight of which collected all AEs, both serious and nonserious. In these eight studies, 1,149 (71%) patients received IV ibuprofen and 452 (28%) received placebo (total N=1,601). Of the 1,149 patients who received at least a single dose of IV ibuprofen, 60% (691) experienced at least one AE. The majority (>90%) of these events were deemed either mild (53%) or moderate (38%) in terms of severity. A greater proportion (85%) of placebo-treated individuals experienced at least one AE, with a similar distribution of severities (mild, 56%; moderate, 38%; severe, 6%). Those events which were experienced by at least 5% of patients in either treatment group are summarized in Table 5.

The most common AEs experienced by members of either treatment group were nausea (IV ibuprofen, 26% vs placebo, 47%), vomiting (IV ibuprofen, 9% vs placebo, 14%), constipation (IV ibuprofen, 7% vs placebo, 14%), and flatulence (IV ibuprofen, 7% vs placebo, 10%). The only AE more frequently experienced by IV ibuprofen-treated subjects was infusion site pain.

AEs reported by elderly patients (≥65 years)

Overall, 66% of patients aged 65 years or older experienced at least one AE, and the majority of these were considered mild or moderate (94%). A greater proportion of patients receiving placebo (94%) experienced AEs as compared to those receiving IV ibuprofen (59%). Those events which were reported by at least 5% of either treatment group are summarized in Table 6.

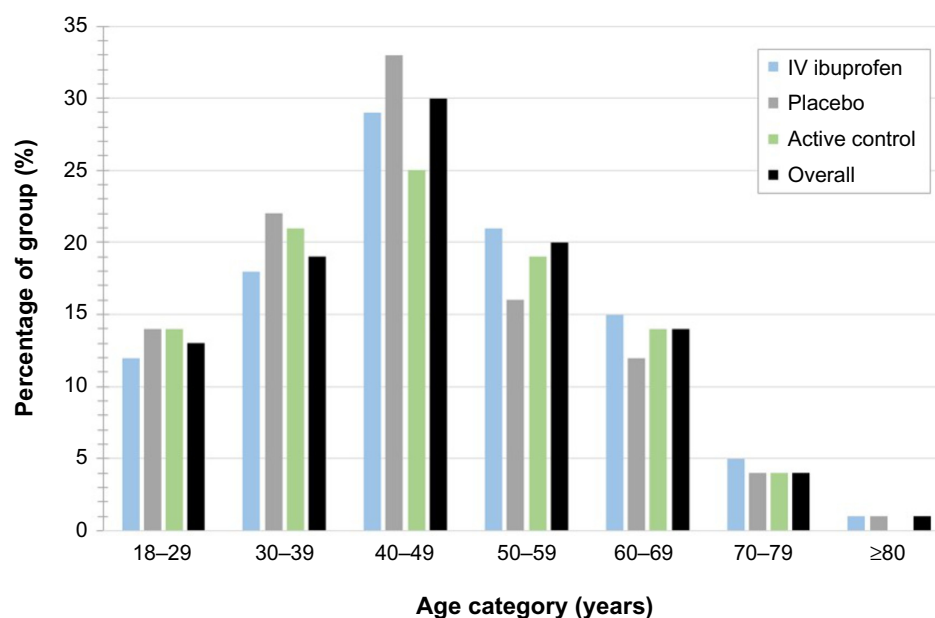


Figure 2 Age distribution by decade.

Abbreviation: IV, intravenous.

The most common AE in patients aged 65 years and older was nausea and was experienced by fewer individuals receiving IV ibuprofen (21%) than those receiving placebo (35%). All individual events occurring in $\geq 5\%$ of elderly patients were less frequent in the IV ibuprofen-treated patients than in the placebo group with the exception of infusion site pain.

Vital signs

Vital signs data were collected in eight studies and quantified as 1) absolute measures, 2) change from baseline, and

3) markedly abnormal (MAVS – ranges given in Methods). The absolute measures and change from baseline were similar between the treatment groups for blood pressure, pulse rate, respiratory rate, and body temperature. The incidence of any MAVS occurring at any point following study drug administration was 19% in the IV ibuprofen group vs 26% in the placebo-treated group. The percentage of patients experiencing any given MAVS was similar in both treatment groups (systolic blood pressure: 9% ibuprofen vs 11% placebo, diastolic blood pressure: 9% ibuprofen vs 14%

Table 4 Cumulative exposure to intravenous ibuprofen by age group

	Intravenous ibuprofen			
	18–64 years (N=1,074)	≥65 years (N=146)		Overall (N=1,220)
Duration of treatment (days)				
Mean (SD)	2 (1.0)	2 (0.8)		2 (1.0)
Median	2	2		2
Range	1–6	1–5		1–6
Total cumulative dose (mg)				
Mean (SD)	2,878 (2,903.2)	2,723 (2,278.9)		2,860 (2,835.3)
Median	2,000	2,400		2,000
Range	100–16,000	500–12,800		100–16,000
Number of doses N (%) ^a	<400 mg (N=61)	400 mg (N=205)	800 mg (N=953)	Overall (N=1,219)
Single dose	1 (2%)	13 (6%)	370 (30%)	384 (32%)
Multiple doses	60 (98%)	192 (94%)	583 (61%)	835 (68%)
2–4	1 (2%)	22 (11%)	208 (22%)	231 (19%)
5–8	59 (97%)	136 (66%)	319 (33%)	514 (42%)
9–12	0	33 (16%)	17 (2%)	50 (4%)
13–20	0	1 (<1%)	39 (4%)	40 (3%)

Notes: ^aNumber and proportion of patients receiving the indicated number of doses per dosing regimen.

Abbreviations: N, number; SD, standard deviation.

Table 5 The most common ($\geq 5\%$) adverse events experienced by adult patients (18–92 years) receiving intravenous ibuprofen or placebo in Phase II–IV studies^a

	IV ibuprofen (N=1,149)	Placebo (N=452)
	N (%) ^b	N (%)
Any adverse event	691 (60)	384 (85)
Nausea	299 (26)	213 (47)
Vomiting	109 (9)	64 (14)
Constipation	85 (7)	62 (14)
Flatulence	77 (7)	44 (10)
Pruritus	72 (6)	65 (14)
Infusion site pain	62 (5)	1 (1)
Headache	59 (5)	37 (8)
Pyrexia	41 (4)	47 (10)
Anemia	50 (4)	23 (5)

Notes: ^aExcludes studies NCT01650519 and NCT01901393 where nonserious AEs were not collected; ^bpercentages less than 1 were rounded to 1.

Abbreviations: N, number; AEs, adverse events; IV, intravenous.

placebo, pulse rate: 5% ibuprofen vs 6% placebo, pulse rate: 2% ibuprofen vs 1% placebo).

Antipyresis

The AE terms “pyrexia” and “body temperature increased” were combined for the purposes of assessing fever as an adverse occurrence. Placebo-treated individuals of either

Table 6 The most common ($\geq 5\%$) adverse events experienced by elderly patients (≥ 65 years) receiving intravenous ibuprofen or placebo in Phase II–IV studies^a

	IV ibuprofen (N=142)	Placebo (N=34)
	N (%) ^b	N (%)
Any adverse event	84 (59)	32 (94)
Nausea	30 (21)	12 (35)
Constipation	19 (13)	7 (21)
Vomiting	14 (10)	6 (18)
Anemia	10 (7)	4 (12)
Hypokalemia	10 (7)	3 (9)
Pyrexia	9 (6)	6 (18)
Infusion site pain	9 (6)	0 (0)
Urine output decreased	7 (5)	4 (12)
Hypertension	7 (5)	2 (6)
Urinary retention	7 (5)	1 (3)
Hypotension	6 (4)	5 (15)
Pruritus	4 (3)	5 (15)
Dyspepsia	2 (1)	2 (6)
Deep vein thrombosis	2 (1)	2 (6)
Dysuria	2 (1)	3 (9)
Anxiety	2 (1)	2 (6)
Atrial fibrillation	1 (1)	2 (6)
Body temperature increased	0 (0)	5 (15)
Muscle spasms	0 (0)	2 (6)

Notes: ^aExcludes studies NCT01650519 and NCT01901393 where nonserious AEs were not collected; ^bpercentages less than 1 were rounded to 1.

Abbreviations: N, number; IV, intravenous; AEs, adverse events.

age group more frequently experienced elevated body temperature than their IV ibuprofen-treated counterparts, with the elderly, placebo-treated individuals experiencing elevated body temperature more frequently than any other group (placebo elderly [32%], placebo adult [13%], IV ibuprofen elderly [6%], and IV ibuprofen adult [5%]).

SAEs and deaths

SAEs are those which result in death, hospitalization, disability, a birth defect, are considered imminently life-threatening, or require medical or surgical intervention to prevent one of the above outcomes. In the ten clinical trials covered by this analysis, 5% of patients (N=81 of 1,752) experienced an SAE. The proportion of patients reporting SAEs was similar in the IV ibuprofen and placebo-treated groups (5% vs 4%). No SAEs were reported in either group in the two surgery studies using active comparator (all knee arthroscopies). No individual SAE occurred in more than 1% of any treatment group, or overall, and most were attributable to the index diagnosis or surgery performed.

A total of eleven deaths occurred in the combined safety population, three in the placebo group (0.6%) and eight in the IV ibuprofen treatment group (0.6%). None of the deaths were deemed related to the study drug by the Investigator at the site, and all deaths were attributable to the underlying medical condition. All of the reported deaths occurred in two studies which enrolled critically ill and/or severely burned patients for the indication of fever.^{13,18} Five deaths (two placebo and three IV ibuprofen) were attributed to respiratory failure or Acute Respiratory Distress Syndrome, and four were attributable to sepsis or complications of sepsis (all IV ibuprofen treated). One IV ibuprofen patient died of multi-organ failure secondary to meningoencephalitis and the remaining placebo patient succumbed to a recurrence of malignancy.

Common side effects of NSAIDs

Hematological effects: AEs and laboratory findings

Sixty-four patients experienced a hemorrhage of any kind, regardless of age or treatment assignment (3.3% of patients receiving IV ibuprofen vs 5.8% of patients receiving placebo) (Table 7). Vaginal hemorrhage (2.6% overall) was the most commonly reported type of bleeding event, which likely reflects the preponderance of gynecological surgeries represented in this analysis (Table 2).

Overall, 73 patients (4.6%) experienced anemia (IV ibuprofen, 4%; placebo, 5%) which was most common in elderly patients receiving placebo (12%) followed by elderly patients receiving IV ibuprofen (7%) (Table 6). Patients aged

Table 7 Incidence of hemorrhages

	IV ibuprofen (N=1,149)		Placebo (N=452)	
	N	%	N	%
Any hemorrhage	38	3	26	6
Vaginal	26	2	16	4
Wound	8	1	4	1
Urethral	1	1	1	1
Incision site	1	1	1	1
Rectal	1	1	0	0
Ear	1	1	0	0
Postprocedural	0	0	2	1
Peritoneal	0	0	1	1
Conjunctival	0	0	1	1

Note: Percentages less than 1 were rounded to 1.

Abbreviations: N, number; IV, intravenous.

18–64 years (or overall) experienced a similar frequency of anemia regardless of treatment (4% ibuprofen vs 5% placebo, Table 5).

An additional analysis of laboratory findings indicated that hematology parameters – hematocrit (Figure 3A), hemoglobin (Figure 3B), and platelet counts (Figure 3C) – were similar between patients receiving IV ibuprofen and those receiving placebo. In summary, no increase in any type of bleeding event or hematological effect was demonstrated in the IV ibuprofen-treated subjects as compared to those receiving placebo when assessed by the AE term or laboratory findings.

Renal effects: AEs and laboratory findings

Overall, a slightly higher proportion of placebo-treated patients (2.4%) experienced an AE in the renal system than did their IV ibuprofen-treated counterparts (1.8%). Average laboratory values commonly used as indicators of renal function – blood urea nitrogen (BUN, Figure 4A) and serum creatinine (SCr, Figure 4B) – were similar between IV ibuprofen and placebo-treated individuals. The incidence of markedly elevated SCr (defined as >2.0 mg/dL) was similar between the IV ibuprofen and placebo groups, but the rate of markedly elevated BUN (defined as >30 mg/dL) was slightly higher in patients receiving IV ibuprofen (3% vs $<1\%$ in placebo).

Other laboratory abnormalities

Overall, the proportion of patients experiencing at least one markedly abnormal lab value was comparable between the IV ibuprofen and placebo-treated groups (67%). The most commonly reported markedly abnormal lab value, albumin <2.0 g/dL, occurred in 7% of the IV ibuprofen

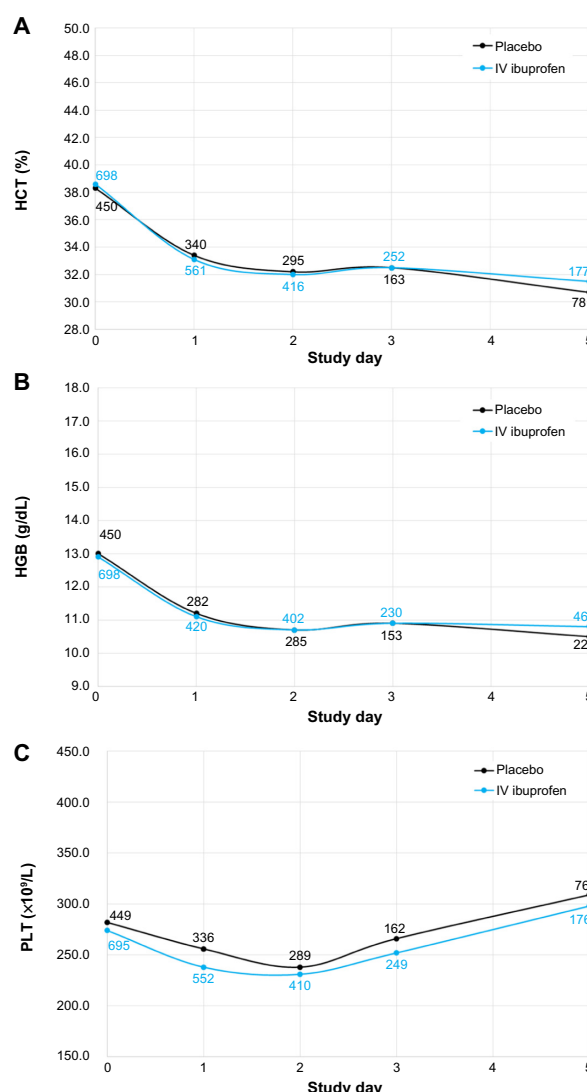


Figure 3 Mean hematology parameters by study day for IV ibuprofen and placebo-treated patients over five days of treatment.

Notes: Day 0= pre-treatment baseline. The sample size for the mean of each treatment group is given for each day. **(A)** Average hematocrit (HCT, %). **(B)** Average hemoglobin (HGB, g/dL). **(C)** Average platelet counts (PLT, cells $\times 10^9/L$).

Abbreviations: HCT, hematocrit; HGB, hemoglobin; IV, intravenous; PLT, platelet counts.

group and 6% of the placebo group. Both groups also reported a similar incidence of elevated alanine aminotransferase (>165 U/L, 2%), aspartate aminotransferase (>150 U/L, 2%), and bilirubin (>2.0 mg/dL, 3%). Elevated white blood cell counts ($>16 \times 10^9/L$) were slightly more frequent in placebo-treated individuals (12%) than in their IV ibuprofen-treated counterparts (9%).

Perioperative dosing

While approved for the management of all types of pain, IV ibuprofen has been studied primarily in surgical models, and the studies included in this analysis have employed

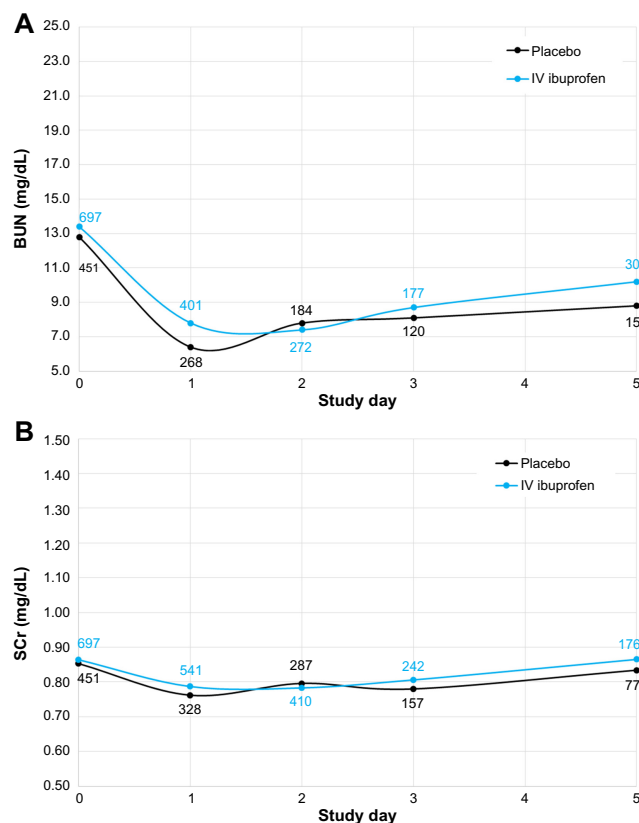


Figure 4 Mean renal parameters by study day for IV ibuprofen and placebo-treated patients over five days of treatment.

Notes: Day 0= pretreatment baseline. The sample size for the mean of each treatment group is given for each day. **(A)** Average blood urea nitrogen (BUN, mg/dL). **(B)** Average serum creatinine (SCr, mg/dL).

Abbreviations: BUN, blood urea nitrogen; SCr, serum creatinine; IV, intravenous.

administration prior to surgery, intraoperative, and post-operative dosing schedules for IV ibuprofen. Two studies of identical design demonstrated that patients receiving 800 mg IV ibuprofen experience less pain and required less post-surgical morphine compared to patients receiving placebo.^{15,16} These studies enrolled patients undergoing elective abdominal or orthopedic surgeries and initiated therapy intraoperatively – prior to wound closure (Figure 5). Study drug was administered every 6 hours, and patients were followed for 24 hours after therapy. A subsequent study was conducted in patients undergoing elective orthopedic surgeries where therapy was initiated at the induction of anesthesia, prior to incision (Figure 5).¹⁷ Dosing frequency, assessments, and follow-up paralleled the studies initiating IV ibuprofen intraoperatively.

The frequency of AEs experienced by subjects beginning their IV ibuprofen therapy prior to incision (proximal to anesthesia induction) was compared to those experienced by subjects beginning their therapy during surgery (before wound closure) (Table 8). Subjects in all three studies who



Figure 5 Timing of the initiation of IV ibuprofen therapy in placebo-controlled, surgical pain studies.

Notes: IV ibuprofen therapy was initiated intraoperatively (prior to wound closure) in Southworth et al¹⁵ and Kroll et al¹⁶. IV ibuprofen therapy was initiated prior to incision (proximal to the induction of anesthesia) in Singla et al.¹⁷

Abbreviation: IV, intravenous.

were randomized to receive IV ibuprofen continued IV ibuprofen therapy in the recovery period; similarly control subjects continued placebo. All three studies were double-blind. Overall, subjects who received preoperative IV ibuprofen therapy experienced a similar frequency of AEs (91%) as those receiving intraoperative IV ibuprofen or placebo (86% and 89%, respectively). Patients did not experience an increase in hemorrhage when IV ibuprofen therapy was initiated prior to surgery (0%, vs 5.6% intraoperative, vs 6.7% placebo). The incidence of GI, CV, and renal AEs was similar regardless of the timing of IV ibuprofen initiation (GI: 58% preoperative, 67% intraoperative, 70% placebo; CV: 6% preoperative, 2% intraoperative, 3% placebo; renal: 13% preoperative, 6% intraoperative, 6% placebo).

Compared to patients receiving placebo, IV ibuprofen-treated patients experienced a 25%–34% reduction in median morphine use when therapy was initiated either intraoperatively or prior to incision (Table 8).

The safety of IV ibuprofen administered prior to surgery has also been evaluated in two controlled, Phase IV studies of

Table 8 Comparable safety of initiating intravenous ibuprofen therapy either prior to surgery or intraoperatively

	Preoperative initiation ^a		Intraoperative initiation ^b	
	Placebo (N=86)	800 mg (N=99)	Placebo (N=287)	800 mg (N=304)
Any adverse event N (%)	74 (86%)	90 (91%)	258 (90%)	260 (86%)
Rescue morphine (mg)				
Mean (SD)	59.5 (29.9)	41.1 (27.3)	52.6 (24.4)	45.7 (29.5)
Median	58.0	38.0	52.8	39.8
P-value ^c	<0.001		<0.001	

Notes: ^aData from Singla et al;¹⁷ ^bcombined data from Southworth et al¹⁵ and Kroll et al;¹⁶ ^csignificance based on the difference in the least squared means from the final ANCOVA model.

Abbreviations: N, number; ANCOVA, analysis of covariance; SD, standard deviation.

patients undergoing elective, outpatient knee arthroscopy and in an uncontrolled, Phase IV study of hospitalized patients undergoing various elective surgical procedures.²⁰ Patients enrolled in the knee arthroscopy studies were followed for SAEs only, and none were reported.^{21,22} The most commonly reported AE in the uncontrolled, Phase IV study was infusion site irritation.

Discussion

Peripheral nociceptors function as the initiation point for the perception of pain.²³ These neurons possess many different cellular receptors, some of which are stimulated by metabolites of the arachidonic acid (AA) pathway.²⁴ Additionally, inflammatory mediators which are released during tissue injury, such as occurs in surgery, can increase the sensitivity of peripheral nociceptors to painful stimuli.²³ NSAIDs inhibit the enzymatic activity of COX1 and COX2, limiting the production of prostaglandins (eg, PGD₂, PGE₂, PGF_{2α}, PGI₂) and thromboxane from AA, but not other downstream AA metabolites such as leukotrienes and lipoxins. Mechanistically speaking, inhibiting the production of prostaglandins and thromboxane eliminates ligands which stimulate peripheral nociceptors to recognize pain and reduces the pro-inflammatory milieu at the wound, or incision, site. NSAIDs also exert antinociceptive effects in the central nervous system and these effects can be the result of central COX inhibition that reduces prostaglandin production in the spinal cord and brain as well as through COX-independent mechanisms (eg, G protein receptor inhibition).^{25,26} Prostaglandin production by spinal COX enzymes has been shown to play a role in the initiation and maintenance of pain perception, and the resulting hyperalgesia can be both prevented and reversed by the administration of NSAIDs including ibuprofen.^{27–29} The establishment of hyperalgesia is likely dependent on COX2 and the production of PGE₂. Using arterial spin labelling imaging of the human brain, the work of Hodkinson et al confirms the analgesic effects of ibuprofen following surgery, demonstrates the activation by ibuprofen of regions in the brain associated with descending pain modulation, and suggests that ibuprofen only exerts central nervous system activity in the presence of inflammatory pain.³⁰ Ibuprofen has also been shown to decrease pain perception in rats following spinal *N*-methyl-D-aspartate receptor activation involving nitric oxide.^{31,32} Cumulatively, data from human and animal studies portray a complex mechanism for the analgesic effects elicited by NSAIDs, particularly ibuprofen, both centrally and peripherally.

The relative extent of COX1 or COX2 inhibition elicited by any given NSAID is also associated with adverse

experiences common to the drug class. Broadly, these adverse experiences are GI, CV, hematological, and renal. As indicated by the reductions in nausea, vomiting, and constipation relative to placebo, GI complications were far less prevalent in the IV ibuprofen-treated population (37%) than in the placebo group (62%, and Table 5). The GI events recorded in these clinical trials, but not summarized in Table 5 (eg, diarrhea, abdominal discomfort, gastritis, etc), occurred at frequencies less than 1% in the IV ibuprofen group. It is unclear whether the reductions in GI complications in the IV ibuprofen group are due to the morphine sparing, analgesic, or anti-inflammatory properties of the drug, but clearly benefit patients regardless of mechanism. Cardiovascular AEs of any type were not highly represented in this analysis. Only 3% of IV ibuprofen-treated patients experienced some type of cardiac event, similar to placebo (2%). With the exception of tachycardia (IV ibuprofen 1%, placebo 2%), no single CV event occurred in as much as 1% of either treatment group. This favorable CV profile may be due to the balanced inhibition of COX1 and COX2 isoenzymes by ibuprofen. Similarly, the cumulative data from the studies included in this analysis demonstrate that there was no increase in anemia or hemorrhagic events and no decrease in hemoglobin, hematocrit, or platelet counts in patients treated with IV ibuprofen relative to those receiving placebo. Additionally, patients receiving IV ibuprofen before surgical incision had a similar rate of bleeding-related events as did those who initiated therapy intraoperatively and both of these were similar to placebo. Finally, the data from this analysis did not indicate an increase in renal impairment in IV ibuprofen-treated individuals as assessed by AE terms, SCr, or BUN levels. Indeed, the only AE that was represented more frequently in the IV ibuprofen-treated group was infusion site pain. Previous studies of IV analgesics demonstrate a rate of infusion site reactions ranging from 5% to 29%.^{33–36} The rate of infusion site reactions in this cumulative analysis (5%) is consistent with other IV non-narcotic analgesics. Administering the drug into a large lumen vein (eg, antecubital vs hand) may decrease infusion site discomfort in subjects who are sensitive to infusions.

The most recent practice guidelines for acute pain management – eg, surgical pain – were released by the American Society of Anesthesiologists (ASA) in 2012. In this guideline, the ASA notes that there are multiple undesirable outcomes resulting from the under-treatment of pain due to surgery. These include thromboembolism, pulmonary complications, extended hospital or intensive care unit length of stay, unplanned readmission for pain

management, suffering, impaired quality of life, and the development of chronic pain syndromes.³⁷ Among the many recommendations made were the preoperative initiation of therapy (a single agent) in anticipation of postoperative pain and the employment, whenever possible, of multimodal techniques (two or more agents, preferably with different mechanisms of action). In the opinion of the ASA, one component of multimodal therapy should be a continual (around-the-clock) NSAID regimen, particularly in the postoperative period, unless otherwise contraindicated. Four studies in this analysis began IV ibuprofen therapy prior to surgical incision and the cumulative safety data indicates that the safety of preoperative dosing is comparable to that of intraoperative and postoperative dosing. This observation suggests that IV ibuprofen could routinely be initiated prior to surgery and continued through the recovery period. For extended surgeries (≥ 6 hours), the anesthesiologist can administer additional doses of IV ibuprofen intraoperatively maintaining prostaglandin inhibition and minimizing postoperative inflammation and pain. Furthermore, the dosage strength of IV ibuprofen can be tailored to the needs of the individual patient as both 400 and 800 mg dosing schedules are included in the product labelling with no limitation on duration. Because improvement in pain as measured by patient-reported VAS score has been demonstrated as a dose-dependent effect,³⁸ the ability to titrate any analgesic to maximize pain relief while minimizing undesirable effects is an important benefit of IV ibuprofen.

The ASA guidelines also address certain patient populations – particularly elderly, the critically ill, or those who are otherwise cognitively impaired. Elderly patients were considered to be more susceptible to the adverse outcomes of under-treatment, and the under-treatment of elderly patients was deemed a widespread phenomenon. No recommendations were made regarding specific agents to be used in elderly populations. It is important to note that elderly patients who received IV ibuprofen also experienced far fewer AEs overall (59%) than did those receiving placebo (94%). In addition to less nausea, vomiting, and constipation, elderly individuals who received IV ibuprofen experienced proportionately less anemia, hypotension, pruritus, dyspepsia, deep vein thrombosis, dysuria, and anxiety than their placebo-treated counterparts. Alleviation of these symptoms is an important consideration in this vulnerable population known to be undertreated.³⁹ Therapies that require self-administration (ie, patient controlled analgesia) were deemed unsuitable for critically ill, cognitively impaired, and communicatively impaired patients. These special groups

may require additional therapies to ensure acceptable pain management. IV ibuprofen is well suited to satisfy many of the recommendations of the ASA including initiation of therapy prior to surgery, continual administration through recovery, elderly use, and controlled administration to critically ill and cognitively impaired patients. The potential benefits of multimodal analgesia include reducing the overall pharmaceutical load on a patient (especially narcotics) thereby increasing the safety of the total anesthesia protocol, decreasing recovery time and hospital stays, and of course, better pain management.²⁴

Narcotics which bind to opioid receptors are prescribed for the treatment of both acute and chronic pain. The common side effects associated with opioid administration are well known and include constipation, nausea, vomiting, sedation, and dizziness. Constipation has been noted to occur with as little as one dose of morphine and may effect up to 95% of patients receiving opioid therapy. Constipation is a potentially serious complication which can result in decreased patient compliance and therefore inferior pain control, hemorrhoid formation, rectal pain, bowel rupture, and potentially death. Less common adverse effects include respiratory depression, reduced gastric motility, bladder dysfunction (eg, urinary retention), immunological depression (both adaptive and innate), hormonal dysfunction (opioid endocrinopathy), sleep disturbances, and CV complications (eg, vasodilation, hypotension, bradycardia). Over time, tolerance, hyperalgesia (increased pain sensitivity), and addiction or physical dependence can develop. It is generally recommended that opioids be used in conjunction with other analgesic approaches (pharmaceutical and otherwise) and for the shortest time possible.⁴⁰ Thus, limiting use of opioid analgesics by any means can increase overall patient safety in the hospital setting. Multiple meta-analyses clearly demonstrate that members of the NSAID drug class confer an opioid sparing effect which is a safety benefit when opioid-associated AEs and the potential for addiction are considered. The extent of the reduction in narcotic use by any given NSAID would be dependent on multiple factors including, but not limited to, the extent of preexisting central sensitization (duration of pain) and the pain level experienced by the patient – even under sedation. Thus, when assessing the extent of morphine sparing reported by a clinical trial, the minimum baseline pain score (eg, VAS) required for eligibility must be taken into account. Due to the nature of the approved indications for IV ibuprofen, clinical studies enroll subjects with mild to moderate pain and above (ie, VAS ≥ 30 mm, 100 mm scale). Alternatively, studies of IV diclofenac or ketorolac

focus on moderate to severe pain and exclusively enroll subjects with a baseline VAS of ≥ 50 mm. Thus, the extent of morphine sparing cannot be compared between the two clinical programs. Alternatively, the conclusion which can be made is that despite the inclusion of a portion of patients with lower baseline pain scores (who may never require narcotics), the use of IV ibuprofen prior to and during surgery is consistently associated with reductions in narcotic use across studies – up to a 74% reduction when integrated into multimodal pain management regimens ($P < 0.001$).²¹ This is a substantial reduction when considered as an absolute value and even more so when the potential dilution of the morphine-sparing effect by inclusion of patients with lower baseline pain is considered.

This analysis demonstrates that IV ibuprofen has a favorable safety profile in comparison to placebo with morphine rescue. In comparison to patients who received placebo, fewer IV ibuprofen-treated patients experience AEs overall (placebo, 85% vs IV ibuprofen 60%). A few of these improvements are consistent with the antipyretic and analgesic effects of NSAIDs, whereas others may indicate potential treatment benefits that go beyond pain and fever reduction, such as opioid sparing and alleviation of inflammatory processes during disease and wound healing.⁴ Indeed, easing the three most common AEs encountered in these trials – nausea, vomiting, and constipation – contributes substantially to patient satisfaction, recovery time, and minimizing the use of other pharmacological agents.⁴¹

Preventing central sensitization is a primary goal of multimodal pain management and NSAIDs have been shown to function both peripherally and centrally in nociception. In the ascending pain cascade, NSAIDs would act at the peripheral nociceptors to eliminate pain-inducing ligands and pro-inflammatory mediators. Additionally, NSAIDs also act centrally both in the spinal dorsal horn, to inhibit PGE₂ production via COX2, and in the brain by activating medullary and cortical (eg, posterior cingulate cortex and orbitofrontal cortex) regions involved in the descending inhibitory pain cascade.^{28,30} An agent such as IV ibuprofen would permit the anesthetist to maintain a constant level of prostaglandin inhibition over the course of a prolonged surgery and to continue that dosing regimen in the postoperative period. To maximize effective analgesia, a multimodal approach – including an agent such as IV ibuprofen that is capable of inhibiting the perception of pain peripherally and centrally in combination with other synergistic analgesics – is likely the best treatment option for many patients.

Conclusion

Overall, IV ibuprofen demonstrates a favorable safety profile resulting in fewer AEs relative to subjects who received placebo with morphine rescue, with the exception of infusion site reactions. In clinical trials, administration of IV ibuprofen has been accomplished in as little as 5–7 minutes and has been administered prior to surgical incision with no increase in AEs relative to patients receiving doses over 30 minutes either intra- or postoperatively. Patients receiving IV ibuprofen require less morphine and experience less pain than do their placebo-treated counterparts with no measurable increases in surgical blood loss, perioperative CV, renal, or respiratory adverse effects. Our results echo those of previously published meta-analyses indicating a low RR for ibuprofen (1.8) vs diclofenac (3.3: 183% increased risk) or ketorolac (11.5: 639% increased risk). Thus, IV ibuprofen can be safely given prior to surgery and continued in the postoperative period as a component of multimodal pain management.

Disclosure

Dr Stephen R Southworth is a consultant for Cumberland Pharmaceuticals Inc. and has served as an investigator and participant in the Speaker Bureau. Amy D Rock PhD, Emily J Woodward PhD, and Alex Peng PharmD are employees of Cumberland Pharmaceuticals Inc., Nashville, TN, USA.

References

1. Caldolor (Ibuprofen) Injection [Package Insert]. Nashville, TN: Cumberland Pharmaceuticals Inc.; 2014.
2. Ketorolac Tromethamine Injection [Package Insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC; 2013.
3. Dyloject™ (Diclofenac Sodium) Injection [Package Insert]. Lake Forest, IL: Hospira, Inc.; 2014.
4. Gallelli L, Galasso O, Falcone D, et al. The effects of nonsteroidal anti-inflammatory drugs on clinical outcomes, synovial fluid cytokine concentration and signal transduction pathways in knee osteoarthritis. A randomized open label trial. *Osteoarthritis Cartilage*. 2013;21(9):1400–1408.
5. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int*. 2012;32(6):1491–1502.
6. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A*. 1999;96(13):7563–7568.
7. Van Hecken A, Schwartz JI, Depre M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. *J Clin Pharmacol*. 2000;40(10):1109–1120.
8. Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med*. 1998;158(1): 33–39.

9. Castellsague J, Riera-Guardia N, Calingaert B, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug Saf.* 2012;35(12):1127–1146.
10. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med.* 2011;8(9):e1001098.
11. Gallelli L, Colosimo M, Pirritano D, et al. Retrospective evaluation of adverse drug reactions induced by nonsteroidal anti-inflammatory drugs. *Clin Drug Investig.* 2007;27(2):115–122.
12. Zusman M. The Absolute Visual Analogue Scale (AVAS) as a measure of pain intensity. *Aust J Physiother.* 1986;32(4):244–246.
13. Morris PE, Promes JT, Guntupalli KK, Wright PE, Arons MM. A multi-center, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for the treatment of fever in critically ill and non-critically ill adults. *Crit Care.* 2010;14(3):R125.
14. Krudsood S, Tangpukdee N, Wilairatana P, et al. Intravenous ibuprofen (IV-ibuprofen) controls fever effectively in adults with acute uncomplicated Plasmodium falciparum malaria but prolongs parasitemia. *Am J Trop Med Hyg.* 2010;83(1):51–55.
15. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clin Ther.* 2009;31(9):1922–1935.
16. Kroll PB, Meadows L, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (iv-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. *Pain Pract.* 2011;11(1):23–32.
17. Singla N, Rock A, Pavliv L. A multi-center, randomized, double-blind placebo-controlled trial of intravenous-ibuprofen (IV-ibuprofen) for treatment of pain in post-operative orthopedic adult patients. *Pain Med.* 2010;11(8):1284–1293.
18. Promes JT, Safcsak K, Pavliv L, Voss B, Rock A. A prospective, multicenter, randomized, double-blind trial of IV ibuprofen for treatment of fever and pain in burn patients. *J Burn Care Res.* 2011;32(1):79–90.
19. Bergese SD, Candiotti K, Ayad SS, Soghomonyan S, Gan TJ. The shortened infusion time of intravenous ibuprofen part 1: a multicenter, open-label, surveillance trial to evaluate safety and efficacy. *Clin Ther.* 2015;37(2):360–367.
20. Gan TJ, Candiotti K, Turan A, et al. The shortened infusion time of intravenous ibuprofen, part 2: a multicenter, open-label, surgical surveillance trial to evaluate safety. *Clin Ther.* 2015;37(2):368–375.
21. Cumberland Pharmaceuticals Inc. A pilot study to determine the efficacy of intravenous ibuprofen for pain control following arthroscopic knee surgery. Available from: <https://clinicaltrials.gov/ct2/show/NCT01650519>. NLM identifier: NCT01650519. Accessed June 30, 2015.
22. Cumberland Pharmaceuticals Inc. Efficacy of intravenous ibuprofen compared to intravenous ketorolac for pain control following arthroscopic knee surgery. Available from: <https://clinicaltrials.gov/ct2/show/NCT01901393?term=NCT01901393&rank=1>. NLM Identifier: NCT01901393. Accessed June 30, 2015.
23. Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. *Am Fam Physician.* 2001;63(10):1979–1984.
24. Kaufman E, Epstein JB, Gorsky M, Jackson DL, Kadari A. Preemptive analgesia and local anesthesia as a supplement to general anesthesia: a review. *Anesth Prog.* 2005;52(1):29–38.
25. Slater D, Kunnathil S, McBride J, Koppala R. Pharmacology of non-steroidal antiinflammatory drugs and opioids. *Semin Intervent Radiol.* 2010;27(4):400–411.
26. Cashman JN. The mechanisms of action of NSAIDs in analgesia. *Drugs.* 1996;52 Suppl 5:13–23.
27. Dirig DM, Isakson PC, Yaksh TL. Effect of COX-1 and COX-2 inhibition on induction and maintenance of carrageenan-evoked thermal hyperalgesia in rats. *J Pharmacol Exp Ther.* 1998;285(3):1031–1038.
28. Yaksh TL, Dirig DM, Conway CM, Svensson C, Luo ZD, Isakson PC. The acute antihyperalgesic action of nonsteroidal, anti-inflammatory drugs and release of spinal prostaglandin E2 is mediated by the inhibition of constitutive spinal cyclooxygenase-2 (COX-2) but not COX-1. *J Neurosci.* 2001;21(16):5847–5853.
29. Freshwater JD, Svensson CI, Malmberg AB, Calcutt NA. Elevated spinal cyclooxygenase and prostaglandin release during hyperalgesia in diabetic rats. *Diabetes.* 2002;51(7):2249–2255.
30. Hodkinson DJ, Khawaja N, O'Daly O, et al. Cerebral analgesic response to nonsteroidal anti-inflammatory drug ibuprofen. *Pain.* 2015;156(7):1301–1310.
31. Bjorkman R. Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Experimental studies in the rat. *Acta Anaesthesiol Scand Suppl.* 1995;103:1–44.
32. Bjorkman R, Hallman KM, Hedner J, Hedner T, Henning M. Nonsteroidal antiinflammatory drug modulation of behavioral responses to intrathecal N-methyl-D-aspartate, but not to substance P and amino-methyl-isoxazole-propionic acid in the rat. *J Clin Pharmacol.* 1996;36(12 Suppl):20S–26S.
33. Jalota L, Kalira V, George E, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ.* 2011;342:d1110.
34. Wininger SJ, Miller H, Minkowitz HS, et al. A randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of two intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. *Clin Ther.* 2010;32(14):2348–2369.
35. Zhou TJ, Tang J, White PF. Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. *Anesth Analg.* 2001;92(6):1569–1575.
36. Moller PL, Juhl GI, Payen-Champenois C, Skoglund LA. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. *Anesth Analg.* 2005;101(1):90–96, table of contents.
37. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology.* 2012;116(2):248–273.
38. Gallelli L, Galasso O, Urzino A, et al. Characteristics and clinical implications of the pharmacokinetic profile of ibuprofen in patients with knee osteoarthritis. *Clin Drug Investig.* 2012;32(12):827–833.
39. Kaye AD, Baluch A, Scott JT. Pain management in the elderly population: a review. *Ochsner J.* 2010;10(3):179–187.
40. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician.* 2008;11(2 Suppl):S105–S120.
41. Kolodzie K, Apfel CC. Nausea and vomiting after office-based anesthesia. *Curr Opin Anaesthesiol.* 2009;22(4):532–538.

Journal of Pain Research

Publish your work in this journal

The Journal of Pain Research is an international, peer-reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication.

Submit your manuscript here: <http://www.dovepress.com/journal-of-pain-research-journal>

Dovepress

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.