Drugs 2012; 72 (8): 1099-1109
0012-6667/12/0008-1099/$55.55/0



# Intravenous Ibuprofen

## In Adults For Pain and Fever

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## Contents



## Abstract

Ibuprofen is a well established analgesic, anti-inflammatory and antipyretic NSAID.

In three double-blind, multicentre trials in postoperative adult patients (n = 185–406), intravenous ibuprofen 800 mg once every 6 hours, as an adjunct to morphine, significantly reduced the consumption of morphine compared with placebo, as an adjunct to morphine, in two of the three trials (primary endpoint in two trials); the between-group difference attained statistical significance in the third trial utilizing a Log-rank transformed analysis. Adjunctive ibuprofen therapy also provided significantly better pain relief during movement than adjunctive placebo for the period from 6 to 24 or 28 hours after the first dose (primary endpoint in one trial).

Furthermore, intravenous ibuprofen plus morphine generally provided better pain relief than placebo plus morphine at all time periods evaluated throughout the first 24 or 28 hours, irrespective of whether this was assessed during rest or movement.

In three double-blind, single- or multicentre trials (n = 60–120) in febrile hospitalized adult patients with acute malaria or with varying causes of fever, intravenous ibuprofen (100–400 mg every 4 or 6 hours, or 800 mg every 6 hours) reduced fever to a significantly greater extent than placebo (primary endpoint in two trials) and/or significantly more patients achieved a temperature of <38.3°C within 4 hours of the first ibuprofen 400 mg dose than with placebo (primary endpoint in the third trial).

Intravenous ibuprofen was generally well tolerated by hospitalized adult patients participating in these clinical trials. The most common adverse event leading to discontinuation of ibuprofen treatment was pruritus (<1% of patients).

| Features and properties of intravenous ibuprofen (Caldolor®) | |
|---|---|
| **Featured indication** | |
| In adults for the management of mild pain, the management of moderate to severe pain as an adjunct to opioid analgesics, and the reduction of fever | |
| **Mechanism of action** | |
| Although the mechanisms of action of ibuprofen are not fully understood, its analgesic, anti-inflammatory and antipyretic effects may be related to inhibition of cyclo-oxygenase isoenzymes, leading to inhibition of prostaglandin synthesis | |
| **Pharmacokinetic profile of ibuprofen 400 mg or 800 mg after a 30- or 60-min infusion in healthy volunteers** | |
| Peak plasma concentration (μg/mL) | 30 min: 39.8 (400); 84.2 (800)<br>60 min: 39.2 (400); 72.6 (800) |
| Elimination half-life (h) | 60 min: 2.2 (400); 2.4 (800) |
| **Dosage and administration** | |
| Infusion duration | No less than 30 min |
| For pain | 400–800 mg every 6 h as required |
| For fever | Initial dose 400 mg, then 400 mg every 4–6 h or 100–200 mg every 4 h as required |
| **Most common treatment-emergent adverse events (incidence ≥5%) in postoperative pain trials** | |
| Nausea, vomiting, haemorrhage, flatulence, headache, dizziness, urinary retention | |

NSAIDs, including ibuprofen, are well established analgesic, antipyretic and anti-inflammatory drugs for use in the clinical setting, including in hospitalized patients.[1,2] Indeed, along with opioids and paracetamol (acetaminophen), NSAIDs form the cornerstone of pharmacotherapy for the treatment of acute and chronic pain.[2] Moreover, based on large meta-analyses of clinical trials, the use of NSAIDs and paracetamol as adjunctive analgesia has been shown to have opioid-sparing effects (reducing morphine consumption by 11–55%) and, as a consequence, to reduce the incidence of opioid-related sedation (by ≈30%) and emetic adverse events (by ≈30%).[3,4] For many patients in the hospital setting such as intubated patients and those experiencing nausea or vomiting, intravenous administration rather than oral administration may be more suitable.[1,5] In addition, intravenously administered agents provide a more rapid onset of action than orally administered agents, since they do not require absorption in the gastrointestinal tract, the rate of which can be variable.[1,5]

Currently, two intravenous NSAIDs are approved for the treatment of pain in the US: ibuprofen (Caldolor®) and ketorolac. Intravenous ibuprofen is approved for use in adult patients for the management of mild pain, management of moderate to severe pain as an adjunct to morphine and the treatment of fever; it may be used peri-operatively except in patients undergoing coronary artery bypass graft (CABG) surgery (section 4).[6] Ketorolac is only approved for use in adults for the management of moderate to severe pain, with the maximum duration of treatment restricted to 5 days; its use prior to surgery and intra-operatively is contraindicated.[7]

This review focuses on the clinical efficacy and tolerability of intravenous ibuprofen in hospitalized adult patients for the treatment of pain and fever, with a brief overview of its pharmacological properties.

Medical literature (published and unpublished data) on the use of intravenous ibuprofen in hospitalized adult patients for the treatment of pain or fever was identified by searching databases (including MEDLINE and EMBASE), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information was also requested from the company developing the drug. Searches were last updated 11 May 2012.

## 1. Pharmacodynamic Properties

- Ibuprofen is a propionic acid derivative that, like other NSAIDs, has analgesic, anti-inflammatory and antipyretic effects.[8] Although the mechanisms of action of ibuprofen are not fully understood,[6] its effects may be related to inhibition of cyclooxygenase isoenzymes (COX-1, the constitutively expressed isoform, and COX-2, the inducible isoform), leading to inhibition of prostaglandin synthesis (mediators of pain and inflammation).[8]
- Ibuprofen causes rapid, reversible, competitive inhibition of both COX-1 and COX-2 isoenzymes.[9,10] In healthy adult volunteers, oral ibuprofen 800 mg three times daily inhibited COX-1 activity by 88.7% and COX-2 activity by 71.4%.[10]
- The selectivity of individual NSAIDs for the COX isoenzymes differs and may determine the likelihood of adverse effects.[8,11] NSAIDs that have a COX-1 : COX-2 inhibition ratio higher than 1 are more likely to be associated with adverse events than NSAIDs that have a ratio of less than 1.[8,10] Inhibition of the COX-1 isoenzyme is generally associated with toxicological effects of NSAIDs, whilst inhibition of the COX-2 isoenzyme is generally associated with the beneficial effects.[8,10]
- Ibuprofen, like many NSAIDs, is a racemic mixture, with *in vivo* and *in vitro* studies indicating that the *S*-enantiomer is responsible for clinical activity.[6,11] The *R*-enantiomer is thought to be pharmacologically inactive and is slowly and incompletely interconverted to the *S*-enantiomer in adults; thus, the *R*-enantiomer acts as a circulating reservoir to maintain levels of active drug.[6]
- In addition to exerting effects via central and peripheral inhibition of COX isoenzymes, ibuprofen may modulate COX-independent signal transduction pathways, including inhibiting the activation of nuclear factor kappa B (a transcription factor that acts as a central mediator of the

immune response), inhibiting neutrophil activity and actions on leukocytes to prevent inflammatory oedema.[9,12]

- COX-independent central antipyretic and analgesic effects of ibuprofen may include potentiating β-endorphin release in response to physiological stress (e.g. during surgery), inhibiting the prevention of spinal release of excitatory amino acids involved in nociception, interfering with G protein-mediated signal transduction, inhibiting the release of arginine vasopressin from the ventral septal area and downregulating nitric oxide production.[9,12-15]

## 2. Pharmacokinetic Properties

- The pharmacokinetic properties of intravenous ibuprofen administered as a 30- or 60-minute infusion in healthy adult volunteers or febrile hospitalized adult patients are summarized in table I.
- In healthy adult volunteers, intravenous ibuprofen was shown to be bioequivalent to intramuscular ibuprofen for both the *S*- and the *R*-enantiomer, as determined by the rate and extent of absorption and the terminal elimination half-life ($t_{½β}$).[17] In addition, there were no clinically significant differences in the pharmacokinetic properties of ibuprofen after a 60-minute intravenous infusion compared with oral administration, except that, as might be expected, maximum plasma concentrations ($C_{max}$) were higher and the time taken to reach these concentrations ($t_{max}$) was faster with intravenous administration.[1]
- In febrile hospitalized patients, the area under the plasma concentration-time curve from zero to 4 hours ($AUC_4$) after the first dose increased in an approximately dose-proportional manner with intravenous ibuprofen 100, 200 and 400 mg (22.33, 32.62 and 70.64 μg • h/mL, respectively) [see section 3 for further discussion of this trial].[16]
- Ibuprofen is highly protein bound (>99% bound at concentrations >20 μg/mL).[6] Protein binding is saturable and is non-linear at concentrations >20 μg/mL.[6]
- After oral administration of ibuprofen, there are age- or fever-related changes in the volume of distribution.[6]

### Optimizing the Infusion Duration

The optimal infusion time for intravenous ibuprofen remains to be fully determined, with the currently approved infusion duration being 30 minutes (section 5). A recent placebo-controlled, cross-over study in 12 healthy adult volunteers investigated single-dose pharmacokinetics of intravenous ibuprofen 800 mg administered as a 5- to 7-minute infusion versus oral ibuprofen 800 mg.[5] These data have also been compared with historical or modelled data for intravenous ibuprofen 400 or 800 mg infused over 30 minutes or 60 minutes (reviewed by Smith and Voss[1]).

- In the cross-over study, a rapid (5–7 minutes) infusion of ibuprofen 800 mg increased mean $C_{max}$ values by 100% compared with oral ibuprofen 800 mg (120 vs 63 μg/mL); as expected, $t_{max}$ was shorter with intravenous administration (0.1 vs 1.5 hours with oral administration).[5] There were no differences between these two

**Table I.** Pharmacokinetic parameters of intravenous ibuprofen in adults. Values are means

| Parameter | In healthy volunteers[a] (30-min;[1] 60-min[6] infusion) | | In febrile hospitalized pts[16] [a] (30-min infusion[b]) | | |
|---|---|---|---|---|---|
| | IBU 400 mg | IBU 800 mg | IBU 100 mg | IBU 200 mg | IBU 400 mg |
| $C_{max}$ (μg/mL) | 39.8; 39.2 | 84.2;[c] 72.6 | NR | NR | NR |
| AUC[d] (μg • h/mL) | NR; 109.3 | NR; 192.8 | 22.3 | 32.6 | 70.6 |
| $t_{½β}$ (h) | NR; 2.2 | NR; 2.4 | NR | NR | NR |

a For studies in healthy volunteers, n = 12/group[6] or not specified; for febrile hospitalized pts, n ≈ 30/group.[16]

b Infusion time reported in a review by Smith and Voss.[1]

c Modelled data.

d AUC time period not specified[1,6] or from time zero to 4 h.[16]

**AUC** = area under the plasma concentration-time curve; **$C_{max}$** = maximum plasma concentration; **IBU** = ibuprofen; **NR** = not reported; **pts** = patients; **$t_{½β}$** = terminal elimination half-life.

routes of administration in terms of mean AUC and $t_{½β}$ values.[5]

- Based on combined data from several trials, with modelled data used where pharmacokinetic values were missing, mean $C_{max}$ values after a 5- to 7-minute, 30-minute or 60-minute infusion of ibuprofen 800 mg were 120, 84.2 and 72.6 μg/mL, respectively; corresponding values after intravenous ibuprofen 400 mg were 59.8, 39.8 and 39.2 μg/mL.[1] Respective $t_{max}$ values with each of these infusion times were 0.1, 0.5 and 1.0 hours after ibuprofen 400 or 800 mg.[1]

In terms of analgesia and antipyresis, the advantage of a more rapid infusion would be a significant shortening of $t_{max}$ times, potentially leading to a faster onset of analgesia than prolonged infusion times or oral ibuprofen.[1] Moreover, relative to oral administration, intravenous administration would eliminate any variability in efficacy associated with variable absorption of the drug in the gastrointestinal tract. This more rapid onset may be particularly important in the perioperative setting and for patients with acute injuries attending an emergency department.[1] Indeed, two surveillance trials are currently underway to evaluate the use of a shortened infusion time for ibuprofen in the treatment of fever or pain in the hospital setting.[18,19]

## 3. Therapeutic Efficacy

This section focuses on the efficacy of intravenous ibuprofen in the treatment of pain or fever in adult patients (aged ≥18 years). Discussion of its use in paediatric patients is beyond the scope of this review. A double-blind, placebo-controlled, multicentre trial[20] in 455 adult patients with sepsis (defined as fever, tachycardia, tachypnoea and acute failure of at least one organ system) formed the rationale for developing an intravenous ibuprofen formulation for use in patients with pain or fever;[21] an indepth discussion of its use in this patient population is beyond the scope of this review. In brief, relative to placebo, intravenous ibuprofen (10 mg/kg; maximum dose 800 mg) significantly ($p < 0.05$) reduced temperature, heart rate, oxygen consumption and lactic acidosis, but did not reduce the incidence or duration of shock or acute respiratory syndrome and had no significant effect on survival rate.[20]

### For Pain

Three large, randomized, double-blind, placebo-controlled, multicentre trials evaluated the therapeutic efficacy of intravenous ibuprofen as adjunctive therapy to morphine for the treatment of postoperative pain in adult patients who underwent elective orthopaedic[22,23] and/or abdominal surgery.[23,24] All patients in these trials received morphine plus adjunctive ibuprofen or placebo. Key trial design details are summarized in table II. Within each trial, there were no significant differences between treatment groups in terms of baseline demographic and clinical characteristics.[22-24] Patients were stratified by age and weight, since the morphine dose is known to directly correlate with these two parameters.[22-24]

Analgesic efficacy endpoints were rated by the patient using a visual analogue scale (VAS; scale of 0–10[24] or 0–100;[22,23] 0 = no pain and 10 or 100 [whichever was the upper limit of the scale] = worst possible pain) and, in one trial,[22] a verbal rating scale (VRS; 0 = no pain and 4 = severe pain). To determine the differences in overall pain at different timepoints, the area under the VAS pain curve ($AUC_{VAS}$) at rest and with movement was analysed for the following time periods: 1–24 hours,[23,24] 6–24 hours[23,24] and 12–24 hours,[23,24] or 6–28 hours.[22]

- In modified intent-to-treat (mITT) populations, morphine consumption was significantly lower in postoperative patients receiving adjunctive intravenous ibuprofen 800 mg every 6 hours than in those receiving adjunctive placebo in two[22,24] of the three[22-24] trials (table III; primary endpoint in two trials[23,24]), as assessed using analysis of covariance (ANCOVA) methods. Where evaluated, there was no difference in morphine consumption between patients receiving adjunctive ibuprofen 400 mg every 6 hours and those receiving adjunctive placebo (table III).[23]
- In the two trials[23,24] in which morphine consumption in the first 24 hours was the primary endpoint, transformation analyses indicated that adjunctive ibuprofen 800 mg, but not ibuprofen

**Table II.** Key design details of randomized, placebo-controlled, multicentre trials (n = 185–406) evaluating adjunctive intravenous ibuprofen for the treatment of postoperative pain in adults who had undergone elective surgery

| Parameter | Kroll et al.[24] | Singla et al.[22] | Southworth et al.[23] |
|---|---|---|---|
| Type of surgery | Total abdominal hysterectomy | Orthopaedic | Orthopaedic or abdominal |
| Inclusion criteria | Aged 18–70 y; anticipated to require IV morphine for >24 h | Aged 18–80 y; anticipated to require IV morphine for ≥28 h post-surgery | Aged 18–70 y; anticipated to require IV morphine for >24 h post-surgery |
| Exclusion criteria | Treatment with any analgesic (except paracetamol up until 6 h before surgery or NSAIDs up until 12 h), muscle relaxant or sedative within 24 h of surgery; weight <30 kg; presence of a medical condition whereby IBU is contraindicated or caution is advised; use of concomitant drugs (e.g. anticoagulants, lithium) that may potentially adversely interact with IBU | Treatment with any analgesic (except paracetamol up until 6 h before surgery or NSAIDs up until 12 h), muscle relaxant or sedative within 12 h of surgery; weight <30 kg; presence of a medical condition whereby IBU is contraindicated or caution is advised; use of concomitant drugs (e.g. anticoagulants, lithium) that may potentially adversely interact with IBU | Treatment with any analgesic (except paracetamol up until 6 h before surgery or NSAIDs up until 12 h), muscle relaxant or sedative within 24 h of surgery; weight <30 kg; presence of a medical condition whereby IBU is contraindicated or caution is advised; use of concomitant drugs (e.g. anticoagulants, lithium) that may potentially adversely interact with IBU |
| Primary endpoint | LSM[a] morphine dose requirement during the first 24 h post-surgery | Pt-assessed (using a VAS) pain upon movement during the period 6–28 h post-surgery | LSM[a] morphine dose requirement during the first 24 h post-surgery |
| Primary efficacy population | mITT[b] | mITT[b] | mITT[b] and EE[c] |

a Adjusted for age (≤45 or >45 y), weight (≤75 or >75 kg), centre and treatment group.

b mITT = pts who received ≥1[22] or a partial[23,24] dose of study medication.

c EE = pts who received ≥4 doses of study medication within 1 h of the scheduled administration time.

**EE** = efficacy evaluable; **IBU** = ibuprofen; **IV** = intravenous; **LSM** = least-square mean; **mITT** = modified intent-to-treat; **pt(s)** = patient(s); **VAS** = visual analogue scale.

400 mg, resulted in a significantly lower consumption of morphine by postoperative patients in mITT analyses (table III). These transformation (log rank[23] or Box-Cox[24]) analyses were conducted because ANCOVA model assumptions of homogeneity of variance were violated.

- Similar trends for a reduction in postoperative morphine consumption with adjunctive ibuprofen 800 mg every 6 hours were observed in the efficacy evaluable (EE) population (coprimary efficacy population in this trial; see table II for definition).[23] The least-square mean (LSM) values for morphine consumption over the first 24 hours in the adjunctive ibuprofen 400 mg (n = 111), ibuprofen 800 mg (n = 116) and placebo (n = 115) groups were 44.7, 42.1 and 48.8 mg, respectively (primary endpoint), as assessed by ANCOVA. After log-rank transformation of data, respective LSM values for morphine consumption were 168.3, 154.5 ($p = 0.026$ vs placebo group) and 184.4 mg.
- In mITT analyses, relative to adjunctive placebo, there were significant ($p < 0.05$) reductions in pain during movement for all timepoints evaluated during the first 24[23,24] or 28[22] hours in adjunctive ibuprofen 800 mg groups and the adjunctive ibuprofen 400 mg group, as assessed by LSM $AUC_{VAS}$ values (table III). In EE analyses for pain with movement, LSM $AUC_{VAS}$ values were significantly ($p < 0.05$) lower in the adjunctive ibuprofen 400 and 800 mg groups than in the adjunctive placebo group for the periods from 6 to 24 hours and from 12 to 24 hours, but not from 1 to 24 hours.[23]
- In addition, in mITT analyses for pain at rest, compared with adjunctive placebo, there were significant ($p \leq 0.01$) reductions in LSM $AUC_{VAS}$ values for all timepoints evaluated (1–24,[23,24] 6–24,[23,24] 6–28[22] and 12–24[23,24] hours) in adjunctive ibuprofen 800 mg groups. With adjunctive ibuprofen 400 mg every 6 hours, there was a significantly greater reduction in LSM $AUC_{VAS}$ values for pain at rest in the adjunctive ibuprofen group than in the adjunctive placebo group during the period from 6 to 24 hours (55.6 vs 59.6 mm/h; $p = 0.013$) and from 12 to 24 hours

**Table III.** Analgesic efficacy of adjunctive intravenous ibuprofen for the treatment of postoperative pain in adult patients who had undergone elective orthopaedic or abdominal surgery. Results from randomized, double-blind, multicentre trials. See table II for further trial design details. Analyses are for the modified intent-to-treat population

| Study | Adjunctive therapy[a] (mg q6 h) [duration; d][b] | No. of pts | Morphine use (mg) | | LSM $AUC_{VAS}$ (mm/h) with movement [between-group difference] | | |
|---|---|---|---|---|---|---|---|
| | | | LSM[c] [median] | Trans LSM[d] | 1–24 h | 6–24[23,24] /28[22] h | 12–24 h |
| Kroll et al.[24] | IBU 800 [2–5] | 166 | 48.7***[e] [43.5] | 12.1*** | [–14%]** | [–20%]*** | [–24%]*** |
| | PL [2–5] | 153 | 57.0[e] [54.0] | 13.6 | | | |
| Singla et al.[22] | IBU 800 [≤5] | 99 | 44.3*** [38.0] | NE | NE | 1005[e,f] [–321.1]*** | NE |
| | PL [≤5] | 86 | 60.9 [58.0] | NE | NE | 1326[e,f] | NE |
| Southworth et al.[23] | IBU 400 [2–5] | 134 | 46.3[e] [44.0] | 208.5 | 116* | 82** | 51** |
| | IBU 800 [2–5] | 138 | 43.8[e] [35.5] | 190.6* | 113** | 79*** | 49*** |
| | PL [2–5] | 134 | 48.9[e] [45.3] | 223.0 | 128 | 93 | 59 |

a All pts received intravenous morphine (1–2 mg every 5 min) via PCA[22-24] or at the pt's request.[24] IBU 60-min infusion[22] or infusion time not specified;[23,24] first dose of IBU given intra-operatively at skin closure.

b As required after d 2.[23,24] Until resolution of pain, removal of intravenous line or hospital discharge.[22]

c ANCOVA with adjustment for age (≤45 or >45 y), weight (≤75 or >75 kg), centre and treatment group.

d Log-rank[23] or Box-Cox[24] transformation. Conducted since ANCOVA model assumptions of homogeneity of variance were violated.

e Primary endpoint.

f Units not specified.

**ANCOVA** = analysis of covariance; **$AUC_{VAS}$** = area under the visual analogue scale pain curve; **IBU** = ibuprofen; **LSM** = least-square mean; **NE** = not evaluated; **PCA** = patient-controlled analgesia; **PL** = placebo; **pt(s)** = patient(s); **q6h** = every 6 h; **trans** = transformed; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PL.

(34.3 vs 35.5 mm/h; $p = 0.005$), but not from 1 to 24 hours (81.7 vs 88.5 mm/h).[23]

- There were generally no significant between-group differences for other secondary endpoints, including rates of treatment failure, time to gastrointestinal motility, time to resumption of ambulation, time to resumption of liquid intake and solid diet, and the length of stay in hospital.[22-24] These studies were not powered to evaluate secondary endpoints.

### For Fever

The antipyretic efficacy of intravenous ibuprofen has been evaluated in three randomized, double-blind trials in hospitalized, febrile adult patients with acute uncomplicated *Plasmodium falciparum* malaria,[25] burns[26] or who were critically or non-critically ill.[16] Key design details are summarized in table IV. Within each trial, there were no significant differences between treatment groups in terms of baseline demographic and clinical characteristics.[16,25,26] In one of these trials,[26] the dosage utilized was higher than that which is recommended for the treatment of fever (see section 5); thus, this study is only briefly discussed.

- In ITT populations, intravenous ibuprofen treatment provided effective antipyretic efficacy in hospitalized, febrile adult patients with burns,[26] those who were critically or non-critically ill[16] and patients with acute uncomplicated malaria.[25] There were significantly greater reductions in the area above 37°C temperature versus time curve (AUC-T°) within the first 24 hours of treatment ($AUC\text{-}T°_{24}$) in ibuprofen groups than in placebo groups (table V; primary endpoint in two[25,26] trials).[16,25,26] The percentage of patients with a temperature of <38.3°C 4 hours after the first dose was also significantly lower in all ibuprofen groups (100–400 mg) than in the placebo group (table V; primary endpoint for ibuprofen 400 mg dose).[16]
- Furthermore, relative to placebo, reductions in fever in hospitalized febrile patients receiving intravenous ibuprofen occurred irrespective of

whether they were defined as critically ill (n = 53 of 120 enrolled patients; 44%) or non-critically ill (n = 67; 56%) at baseline.[16]

- In other secondary analyses in the ITT population, there were no significant between-group differences in the mean time to treatment failure or the mean temperature decrease at 24 hours in this study.[16]
- Reductions in LSM AUC-T° values in febrile patients with burns receiving ibuprofen 800 mg every 6 hours were sustained for the entire 120-hour treatment period (LSM AUC°$T_{120}$ 48.4 vs 55.8 in the placebo group; units not specified).[26] Apart from during the first 24 hours (table V), there was no significant between-group difference in LSM AUC-T° values.
- In febrile patients with acute uncomplicated malaria, reductions in the mean AUC-T° for the first 4 hours (2.4 vs 5.18; $p < 0.0001$; no units specified) and for the entire 72-hour (8.85 vs 16.94; $p = 0.02$) treatment period were also significantly greater with ibuprofen 400 mg every 6 hours than with placebo.[25] There was no between-group difference in mean AUC-T° values for the period from 24 to 72 hours.
- The time for the temperature to fall below 37°C in febrile patients with acute uncomplicated malaria was numerically shorter in the ibuprofen group than in the placebo group (table V; no statistical data reported).[25] There was no statistically significant between-group difference for this parameter in febrile patients with burns (table V).[26]
- Very few participants in any treatment group experienced pyrexia treatment failure (table V; see table for definition).[25,26]

## 4. Tolerability

- Intravenous ibuprofen was generally well tolerated in patients participating in clinical trials discussed in section 3,[16,22-26] including the study in patients with sepsis.[20] Discussion in this

**Table IV.** Key design details of randomized, placebo-controlled, single-[25] or multicentre[16,26] trials (n = 60–120) evaluating intravenous ibuprofen for the treatment of fever in hospitalized adult patients

| Parameter | Krudsood et al.[25] | Morris et al.[16] | Promes et al.[26] |
|---|---|---|---|
| Pt population | Acute uncomplicated *Plasmodium falciparum* malaria | Critically[a] and non-critically ill pts | Pts in a thermal burns unit |
| Inclusion criteria | Aged >17 y; had an oral temperature of >38°C; have been febrile for ≥12 h | Aged ≥18 y; fever developed in previous 7 d; had a temperature of ≥38.3°C | Paediatric[b] and adult pts; second- or third-degree burns covering >10% of TBSA (including face); anticipated hospital stay >72 h; fever ≥38°C |
| Exclusion criteria | Antipyretic medication within 8 h of study treatment; weight <40 kg; pregnant or breast-feeding; presence of any features of severe malaria or any other significant additional medical problems | Antipyretic medication within 4 h of study treatment; weight <40 kg; presence of a medical condition whereby IBU is contraindicated or caution is advised; use of concomitant drugs (e.g. anticoagulants, lithium) that may potentially adversely interact with IBU | Electrical burns; antipyretic medication within 4 h of study treatment; presence of a medical condition whereby IBU is contraindicated or caution is advised; use of concomitant drugs (e.g. anticoagulants, lithium) that may potentially adversely interact with IBU |
| Primary endpoint | Clinical response of fever, assessed as AUC-$T°_{24}$ | Percentage of pts with a temperature of <38.3°C 4 h after the first dose of IBU 400 mg or placebo | Clinical response of fever, assessed as AUC-$T°_{24}$ |
| Primary efficacy population | ITT[c] | ITT[c] | ITT[c] |

a Pts who required mechanical ventilation for respiratory failure and/or pressor support for hypotension.

b Pts <18 y of age were eligible for enrolment, although no pts in this age group were enrolled.

c All randomized pts.

**AUC-$T°_{24}$** = area above 37°C temperature versus time curve within the first 24 h of treatment; **IBU** = ibuprofen; **ITT** = intent to treat; **pt(s)** = patient(s); **TBSA** = total body surface area.

**Table V.** Antipyretic efficacy of intravenous ibuprofen in hospitalized adult patients with burns[26] or acute uncomplicated *Plasmodium falciparum* malaria infection,[25] or who were critically or non-critically ill.[16] Results from randomized, double-blind, placebo-controlled, single-[25] or multicentre[16,26] trials. See table IV for further design details. Analyses were conducted in the intent-to-treat population

| Study | Treatment[a] (mg) [duration; d] | No. of pts | LSM AUC-T°$_{24}$[b] | Responders[c] (% of pts) | Mean time to temp of <37°C (h) | Pyrexia treatment failure[d] (% of pts) |
|---|---|---|---|---|---|---|
| Krudsood et al.[25] | IBU 400 q6 h [3] | 30 | 7.49**[e] | NE | 3 | 7 |
| | PL [3] | 30 | 16.44[e] | NE | 20 | 10 |
| Morris et al.[16] | IBU 100 q4 h [1] | 31 | [f] | 61* | NE | NE |
| | IBU 200 q4 h [1] | 30 | [f] | 70*** | NE | NE |
| | IBU 400 q4 h [1] | 31 | [f] | 77***[e] | NE | NE |
| | PL [1] | 28 | [f] | 32 | NE | NE |
| Promes et al.[26] | IBU 800[g] q6 h [5] | 40 | 12.21**[e] | NE | 1.6 | 3 |
| | PL [5] | 21 | 18.29[e] | NE | 3.1 | 10 |

a 30-min infusion[25,26] or infusion time not specified.[16]

b Units not specified.

c Pts achieving a temp <38.3°C 4 h after the first dose.

d Pts with a temp >41.1°C during the period ≥2 h after the first dose or >39.4°C during this period after the 2nd or subsequent doses.

e Primary endpoint.

f AUC-T°$_{24}$ values significantly lower for all active treatments; no p values or AUC-T°$_{24}$ values reported.

g Dosage recommended for analgesia but not for fever (section 5).

**AUC-T°$_{24}$** = area above 37°C temperature versus time curve within the first 24 h of treatment; **IBU** = ibuprofen; **LSM** = least-square mean; **NE** = not evaluated; **PL** = placebo; **pts** = patients; **qxh** = every x h; **temp** = temperature; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL.

section focuses on pooled analyses of tolerability data from some[16,23-25] of these clinical trials, as reported in the US manufacturer's prescribing information.[6]

- In pooled analyses, the majority of patients receiving intravenous ibuprofen or placebo experienced at least one treatment-emergent adverse event in clinical trials evaluating its use in the treatment of postoperative pain (88% [400 mg ibuprofen/dose; n = 134] and 86% [800 mg ibuprofen/dose; n = 304] of patients in the ibuprofen groups and 90% of patients in the placebo group [n = 287]) or fever (74–87% [100–400 mg ibuprofen/dose; n = 91] and 89% [placebo; n = 28]).[6]
- Overall, the most common treatment-emergent adverse events occurring in at least 10% of patients during intravenous ibuprofen treatment in analgesia clinical trials were nausea, flatulence, haemorrhage, vomiting and headache (figure 1), with dizziness and urinary retention occurring in at least 5% of patients.[6] The most common adverse event leading to treatment discontinuation was pruritus (<1% of patients).
- In fever studies in febrile, hospitalized adult patients with malaria or varying causes of fever, treatment-emergent adverse events that occurred in ≥10% of patients are summarized in figure 1.[6] Those occurring in at least 20% of patients in any individual treatment group were anaemia and eosinophilia (figure 1).
- As with all NSAIDs, ibuprofen may increase the risk of serious cardiovascular thrombotic events, myocardial infraction or stroke, some of which may be fatal.[6] The risk of such events may increase with the duration of NSAID use. Controlled clinical trials of COX-2-selective NSAIDs for the treatment of pain in the first 10–14 days following CABG surgery demonstrated an increased incidence of myocardial infarction and stroke.[6]
- NSAIDs, including ibuprofen, may cause serious and potentially fatal gastrointestinal adverse events, including inflammation, bleeding, ulceration and perforation of the stomach, small or large intestine.[6] These events occur in approximately 1% of patients treated with NSAIDs for 3–6 months and 2–4% of patients treated for longer periods.[6]
- In clinical trials, elevations of ALT or AST levels of approximately ≥3 × the upper limit of normal were reported in approximately 1% of patients receiving NSAIDs.[6] There have also

been rare and potentially fatal cases of severe hepatic reactions, including jaundice, fulminant hepatitis, liver necrosis and hepatic failure.[6]

- Treatment with NSAIDs, including ibuprofen, may lead to the onset of new hypertension or worsening of pre-existing hypertension, which in turn, may contribute to the increased incidence of cardiovascular events.[6] Some patients experience fluid retention and oedema during NSAID treatment; as with other NSAIDs, ibuprofen should

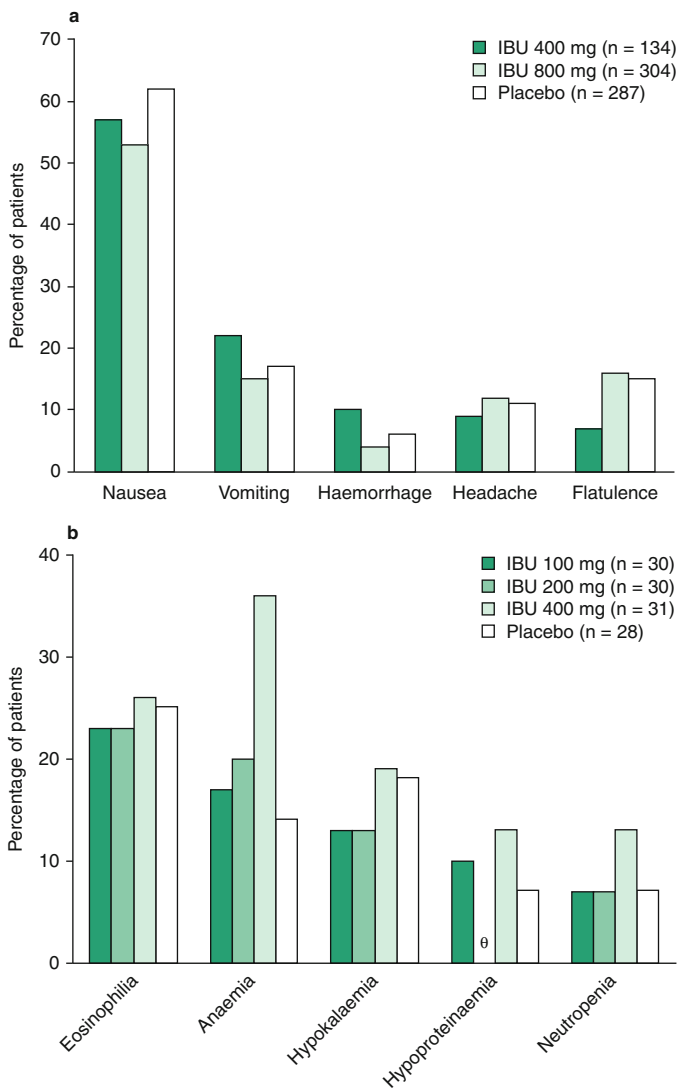


**Fig. 1.** Tolerability of intravenous ibuprofen in hospitalized adult patients participating in randomized, double-blind, placebo-controlled trials. Pooled analyses of treatment-emergent adverse events occurring with an incidence of ≥10% in any ibuprofen group in clinical trials evaluating the use of intravenous ibuprofen for the treatment of (**a**) postoperative pain or (**b**) fever, as reported in the US manufacturer's prescribing information.[6] In analgesia trials, patients received adjunctive ibuprofen 400 or 800 mg or placebo once every 6 hours for ≥2 days (see table II for design details of individual trials;[23,24] all patients also received morphine). In fever trials, febrile patients with acute uncomplicated malaria or with varying causes of fever received ibuprofen 100, 200 or 400 mg or placebo once every 4 or 6 hours for up to 3 days (see table IV for design details of individual trials[16,25]). **IBU** = ibuprofen; θ = incidence of 0%.

be used with caution in patients with fluid retention or heart failure.[6]

- Ibuprofen, like other NSAIDs, may cause serious and potentially fatal skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis; treatment should be discontinued if rash or other signs of local skin reaction occur.[6]

## 5. Dosage and Administration

In the US, the recommended dosage of intravenous ibuprofen for the treatment of pain is 400 or 800 mg every 6 hours as required; in febrile patients, the initial dose of ibuprofen is 400 mg, followed by 400 mg every 4 to 6 hours as required or 100–200 mg every 4 hours as required.[6] Intravenous ibuprofen is given as a 30-minute infusion; patients must be well hydrated prior to the infusion of ibuprofen.

Ibuprofen is contraindicated in patients with asthma, urticaria or allergic-type reactions after taking aspirin or any other NSAIDs.[6] It is also contraindicated during the perioperative period of CABG surgery (see section 4).[6] Ibuprofen should be used with caution in patients with a prior history of ulcer disease or gastrointestinal bleeding (see section 4). Since hypertension may occur during NSAID treatment (see section 4), BP should be monitored during treatment.[6] Discontinue treatment immediately if abnormal liver tests persist or worsen (see section 4).[6] Since long-term treatment with NSAIDs may result in renal papillary necrosis and other renal injury, ibuprofen should be used with caution in patients at risk of such events (e.g. the elderly, those with renal impairment, heart failure or hepatic impairment, and patients taking diuretics or ACE inhibitors).[6]

Local prescribing information should be consulted for details on any other warnings, precautions and potential drug interactions.

## 6. Intravenous Ibuprofen: Current Status in Pain and Fever

In the US, intravenous ibuprofen is indicated for use in adults for the management of mild pain, the management of moderate to severe pain as an adjunct to opioid analgesics and for the reduction of fever.[6] In randomized, double-blind trials, intravenous ibuprofen 800 mg once every 6 hours, as an adjunct to morphine, provided effective treatment for postoperative pain and reduced the consumption of morphine compared with placebo plus morphine in adult patients who had undergone orthopaedic or abdominal surgery. In similarly designed trials in febrile, hospitalized adult patients with malaria or varying causes of fever, intravenous ibuprofen resolved fever to a significantly greater extent than placebo. Intravenous ibuprofen was generally well tolerated in these patients, with the most common treatment-emergent adverse events in analgesia trials being nausea, vomiting, haemorrhage, flatulence, headache, dizziness and urinary retention.

Ongoing clinical trials are evaluating the use of intravenous ibuprofen in adult patients undergoing inguinal hernia repair[27] or electroconvulsive therapy[28] and in adult patients requiring treatment for migraine headache.[29] Clinical trials are also underway to evaluate the use of intravenous ibuprofen in paediatric patients for the treatment pain[30] or fever.[31]

## Acknowledgements and Disclosures

The manuscript was reviewed by: ***P. Azari***, Department of Anesthesia and Pain Management, Duke University, Durham, NC, USA; ***R.L. Barkin***, Rush Medical College, Rush University Faculty of Anesthesiology, Family Medicine and Pharmacology, Skokie, IL, USA; ***A.S. Habib***, Department of Anesthesiology, Duke University Medical Centre, Durham, NC, USA.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit.

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