REVIEW ARTICLE

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Pharmacokinetics of Intravenous Ibuprofen

Implications of Time of Infusion in the Treatment of Pain and Fever

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Contents

Abstract

Intravenous NSAIDs are playing an increasingly large role in analgesia, anti-inflammation and antipyresis in the hospitalized setting. For many years, ketorolac was the only intravenous NSAID available in the US, but in 2009 intravenous ibuprofen was approved by the US FDA for the treatment of pain and fever in adults. In developing intravenous ibuprofen, a range of times of infusion and dosing levels have been utilized and compared with the oral route of administration. The earliest studies utilized a 60-minute infusion, and later a 30-minute infusion was used for the pivotal/registration studies demonstrating efficacy and safety. Another recent trial in healthy volunteers demonstrated a safe and tolerable rapid infusion (5–7 minute) of intravenous ibuprofen. The pharmacokinetic data from all of the clinical trials on 400 and 800 mg doses of intravenous ibuprofen were compiled, and pharmacokinetic modelling was utilized to simulate any data not acquired in the clinical studies. The pharmacokinetic profile of the following doses was modelled: 30-minute infusion of 800 mg intravenous ibuprofen, 5- to 7-minute infusion of 400 mg intravenous ibuprofen and 400 mg ibuprofen oral tablet. These pharmacokinetic analyses revealed that, in general, maximum plasma concentration (C_{max}) decreases considerably as the length of the infusion increases and that an oral dose is not able to achieve the C_{max} level of any intravenous dose. For the rapid infusion, C_{max} was twice that of the oral dose and, as expected, time to C_{max} (t_{max}) was much more rapid than with the oral dose. However, the oral dose still maintained virtually 100% oral

bioavailability. The efficacy of intravenous ibuprofen in terms of pain and fever has also been studied and this review found the drug to be efficacious for both indications. Future areas of study should include assessment of the analgesic and antipyretic efficacy of a rapid (5- to 10-minute) infusion and further assessment of pre-emptive administration of intravenous ibuprofen as part of a multimodal analgesic approach in the surgical setting.

1. Background

In June 2009, the US FDA approved intravenous ibuprofen (Caldolor®, Cumberland Pharmaceuticals Inc.) for the treatment of mild to moderate pain, moderate to severe pain as an adjunct to opioids and fever in adult patients.[1] Prior to the approval of intravenous ibuprofen, the only intravenous NSAID available in the US was intravenous ketorolac, which is only approved for the treatment of moderate to severe pain in the postoperative setting.

Intravenous ibuprofen was initially developed and studied as a possible therapy for sepsis patients.[2] Although an experimental formulation of intravenous ibuprofen did not have an effect on mortality rate, intravenous ibuprofen did reduce inflammatory marker levels (prostacyclin and thromboxane), lactic acid levels, heart rate and oxygen consumption, as well as having a significant antipyretic effect in these patients.[2] These findings led to the further study and commercial development of intravenous ibuprofen as an analgesic and antipyretic for use in patients who could not take oral medications or where intravenous administration was preferable.

A growing body of clinical trial data evaluating the pharmacokinetics, efficacy and safety of intravenous ibuprofen in adult patients is currently available.[2-10] As occurs with most pharmaceutical products, the dosing continues to be studied through clinical trials and prescribed use in the hospital/clinic setting.

This article reviews existing clinical trial results, highlights additional post-marketing findings and postulates how new dosing strategies may further improve the analgesic and antipyretic effects of intravenous ibuprofen by altering the pharmacokinetic/pharmacodynamic relationship.

2. Pharmacokinetics of Intravenous Ibuprofen

The phase I study of intravenous ibuprofen in adults confirmed that the pharmacokinetics of 200, 400 and 800 mg doses of oral (Advil® Liqui-Gel) and a 60-minute infusion of intravenous ibuprofen were comparable, with no clinically significant differences found between the two routes of administration.[11]

An infusion time of 30 minutes was selected for the clinical efficacy studies and is currently listed on the product labelling.[1,3-6] In a pivotal fever study, additional pharmacokinetic analyses were completed.[6] In this multicentre placebo-controlled study, 120 febrile adults received 100 mg, 200 mg or 400 mg intravenous ibuprofen or placebo, administered every 4 hours for 24 hours of treatment, and plasma samples for pharmacokinetic analysis were obtained from the first 98 subjects enrolled in the study.[6] The following pharmacokinetic parameters were determined for each patient: area under the plasma concentration-time curve from hour 0 to hour 4 for dose 1 (AUC_4), the maximum plasma concentration of drug (C_{max}) after the first dose (over the interval from hour 0 to hour 4; $C_{max\text{-}dose1}$) and time to $C_{max\text{-}dose1}$ ($t_{max–dose1}$).[6] The AUC_4 was approximately dose proportional for the 200 mg and 400 mg dose levels of intravenous ibuprofen.[6] The dose normalized AUC_4 was somewhat greater for the lower dose level of 100 mg intravenous ibuprofen than for the higher dose levels, possibly due to slight undetectable differences in disease severity among the study cohorts.[6] This study was stratified by severity of illness (critically ill vs non-critically ill), where critically ill patients were defined as receiving vasopressor support and/or mechanical ventilation.[6] This stratification

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revealed a difference in pharmacokinetics based on the severity of illness.[6] The C_{max} and AUC for all doses of intravenous ibuprofen were significantly reduced in critically ill patients when compared with non-critically ill patients, while the pharmacokinetics remained first order in both patient populations.[6] These differences are thought to be related to a larger volume of distribution that can be seen with some drugs in the critically ill population.[12]

More recently, an additional phase I study was conducted to assess the pharmacokinetics, safety and tolerability of a rapid infusion (5–7 minutes) of intravenous ibuprofen.[8] In this single-centre, placebo-controlled, single-dose crossover study, 12 healthy adult subjects were administered a single dose of 800 mg ibuprofen (oral ibuprofen with intravenous placebo followed by a 5-day washout period and crossover to a rapid infusion of intravenous ibuprofen with oral placebo, or *vice versa*).[8] The pharmacokinetic parameters were observed to be similar when a single dose of 800 mg ibuprofen was administered either intravenously or orally, except for C_{max}, which was twice that of the oral dose, and, as expected, t_{max} was achieved much more rapidly than with the oral dose.[8] In addition, tolerability assessments and adverse event monitoring were performed regularly throughout the treatment period.[8] Intravenous ibuprofen appeared to be safe and well tolerated when appropriately diluted and administered over 5–7 minutes.[8]

The combined pharmacokinetic parameters from the package labelling and these clinical trials are listed in table I and illustrated in figure 1a–b for 800 and 400 mg doses of ibuprofen, respectively. Not all of the clinical trials studied both the 800 and the 400 mg doses of intravenous ibuprofen or the varying times of infusion. Therefore, compiling and comparing the data for each time of infusion of each dose level revealed some data that had not been gathered. Pharmacokinetic modelling was completed to simulate any data that were not gathered in the intravenous ibuprofen pharmacokinetic studies and these data are also shown in table I and figure 1a–b (dashed lines). These simulations were completed using the Simulation Function in Phoenix WinNonlin® software (version 6.0.1, Pharsight, Mountain View, CA, USA) and existing intravenous ibuprofen pharmacokinetic data. For the intravenous infusion simulations, the 5- to 7-minute infusion data were fitted to a two-compartment model with constant intravenous input. For the oral simulation, the 800 mg oral tablet data were fitted to a one-compartment model with first-order absorption and first-order elimination. Previous studies have found oral ibuprofen to fit a two-compartment model, but the current oral data proved to better fit a one-compartment model, likely due to a more narrow time range of available blood levels.[8,13] The pharmacokinetic profile of the following doses was modelled: 30-minute infusion of 800 mg intravenous ibuprofen, 5- to 7-minute infusion of 400 mg intravenous ibuprofen and 400 mg ibuprofen oral tablet. In addition, for the 30-minute infusion of intravenous ibuprofen, the 1.5-hour timepoint was interpolated and the 5-, 6-, 8-, 10- and 12-hour timepoints were extrapolated using the patient data obtained from hours 0 through 4 in the aforementioned clinical study.[6]

Figure 1a illustrates the pharmacokinetic profiles of a single dose of 800 mg intravenous ibuprofen infused over 5–7 minutes, as well as single doses infused over 30 and 60 minutes, compared

Table I. Pharmacokinetic values for a single dose of 800 mg or 400 mg intravenous ibuprofen infused over 5–7, 30 or 60 minutes compared with a single oral dose. Data are presented as mean ± SD, or mean (coefficient of variation), and were compiled from several different studies for comparison

Ibuprofen dose and time	C_{max} (μg/mL)	t_{max} (h)
800 mg		
IV-IB 5–7 min infusion	120 ± 13	0.11 ± 0.01
IV-IB 30 min infusion	84.17[a]	0.54[a]
IV-IB 60 min infusion	72.6 (13.2)	1.0
Oral tablet	63 ± 12	1.50 ± 0.58
400 mg		
IV-IB 5–7 min infusion	59.76[a]	0.1[a]
IV-IB 30 min infusion	39.8 ± 17.8	0.5
IV-IB 60 min infusion	39.2 (15.5)	1.0
Oral tablet	30.3[a]	1.62[a]

a Modelled data.

C_{max} = maximum plasma concentration; **IV-IB** = intravenous ibuprofen; **min** = minute; **t_{max}** = time to C_{max}.

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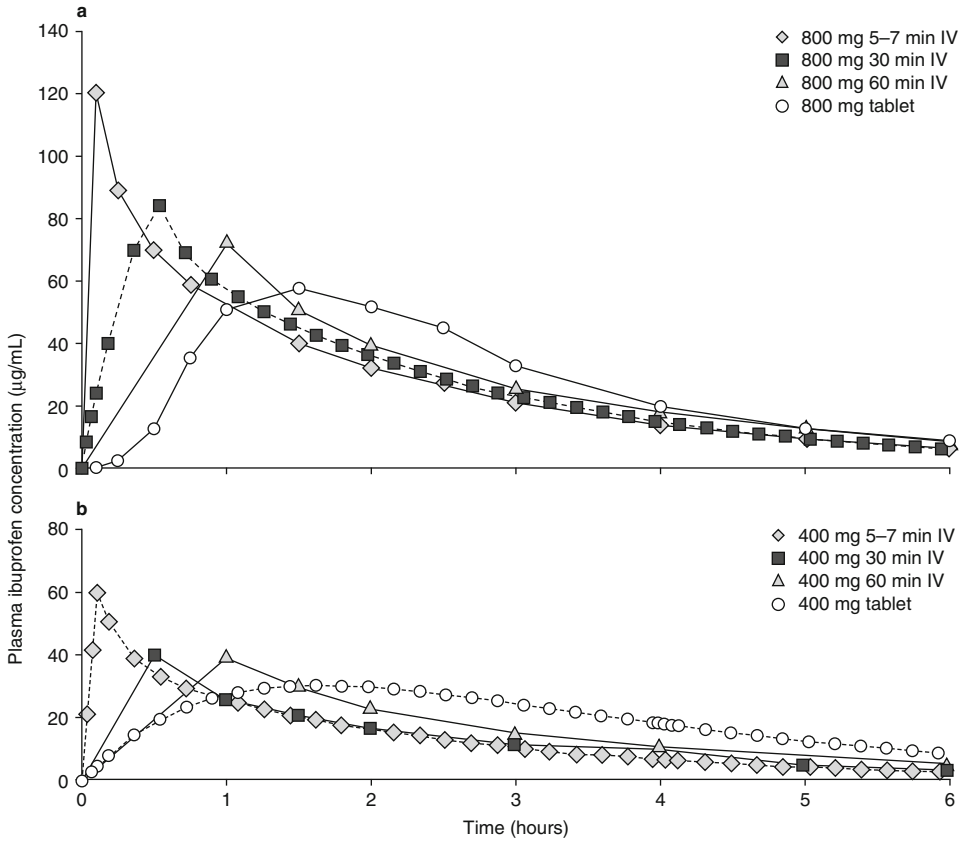

Fig. 1. Pharmacokinetic profile of a single dose of (**a**) 800 mg or (**b**) 400 mg intravenous ibuprofen infused over 5–7, 30 or 60 minutes compared with a single oral dose. Solid line denotes patient data. Dashed line denotes modelled data. **IV** = intravenous; **min** = minute.

with a single 800 mg oral dose of ibuprofen. These data reveal that C_{max} decreases considerably as the length of the infusion increases and that an oral dose is not able to achieve the C_{max} level of any intravenous dose (table I). Another group of researchers have studied a rapid infusion of a different formulation of intravenous ibuprofen, which utilizes the lysine salt as a buffer instead of the arginine salt.[14] Oral bioavailability of ibuprofen is known to be nearly 100% and figure 1a confirms comparable bioavailability of all intravenous doses with oral.[13] Taken together, these data represent the first compilation and comparison of the pharmacokinetics of intravenous ibuprofen administered over different periods of time.

Per the product labelling 100, 200 and 400 mg intravenous ibuprofen are the recommended doses for reduction of fever.[1] Figure 1b illustrates the pharmacokinetic profiles of a single dose of 400 mg intravenous ibuprofen infused over 5–7, 30 or 60 minutes compared with a single 400 mg oral dose of ibuprofen. These data reveal a C_{max} approximately half that of the 800 mg intravenous ibuprofen dose for all infusion times and show a similar inverse relationship between C_{max} and infusion time (table I). Similar to the 800 mg oral dose, the C_{max} of 400 mg oral ibuprofen was lower than any of the intravenous doses and all of the intravenous doses had comparable bioavailability to the oral dose (table I).

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3. Clinical Efficacy of Intravenous Ibuprofen

3.1 Pain

Two independent studies were designed to gather the pivotal/registration analgesic data required for a pain indication with US FDA, and an additional pre-emptive analgesic study was completed to complement the two pivotal studies.[3-5] First, the analgesic effects of a range of doses of intravenous ibuprofen were studied in a multicentre placebo-controlled trial in adult patients in the post-operative setting (table II).[3] In this study, 406 patients who had undergone elective abdominal or orthopaedic surgery were randomized to receive intravenous ibuprofen 400 mg or 800 mg, or placebo, via 30-minute infusions administered every 6 hours.[3] Compared with placebo, there was a 26% reduction in the use of morphine through 24 hours in patients receiving 800 mg intravenous ibuprofen ($p < 0.05$).[3] In addition to the morphine-sparing effect, compared with placebo, patients receiving 800 mg intravenous ibuprofen experienced a greater reduction in pain as measured by the visual analogue scale (VAS) area under the curve for the first 24 hours after surgery ($p < 0.001$).[3] The 400 mg

Table II. Pharmacodynamic studies of intravenous ibuprofen for treatment of pain

Study, year of publication	Pt type	n	Design	Primary endpoint	Conclusion
Southworth et al.,[3] 2009	Adult elective abdominal or orthopaedic surgery	406	Multicentre, PL-controlled, 1 : 1 randomization	Post-operative morphine use	Significant ↓ in morphine use through 24 h in pts receiving 800 mg IV-IB vs PL
Kroll et al.,[4] 2011	Adult elective abdominal hysterectomy	319	Multicentre, PL-controlled, 1 : 1 randomization	Post-operative morphine use	Significant ↓ in morphine use through 24 h in pts receiving 800 mg IV-IB vs PL
Singla et al.,[5] 2010	Adult orthopaedic surgery	185	Multicentre, PL-controlled, pre-operative administration, 1 : 1 randomization	Pain with movement following surgery	Significant ↓ in pain with movement following surgery in pts receiving 800 mg IV-IV vs PL
Promes et al.,[9] 2011	Adult thermal burn	61	Multicentre, PL-controlled, 2 : 1 randomization	AUC-T° over the first 24 h of tx	IV-IB significantly reduced AUC-T° for 0–24 h
Cumberland Pharmaceuticals[15]	Adult pain or fever	150	Multicentre, open-label surveillance trial	Safety of a single dose of IV-IB administered over 5–10 min	Currently enrolling
Cumberland Pharmaceuticals[16]	Adult post-operative pain	300	Multicentre, open-label surgical surveillance trial	Safety of a single dose of IV-IB administered over 5–10 min pre-operatively	Currently enrolling
St. Barnabas Medical Centre[17]	Adult inguinal hernia repair	100	Single-centre, PL-controlled, 1 : 1 randomization	Post-operative narcotic analgesic use	Currently enrolling
University of Medicine and Dentistry of NJ[18]	Adult electroconvulsive therapy	40	Single-centre, PL-controlled, 1 : 1 randomization	Post-electroconvulsive therapy pain	Currently enrolling
Thomas Jefferson University[19]	Adult migraine headache	120	Single-centre, PL-controlled, 1 : 1 randomization	Pain relief in first 2 h following tx	Currently enrolling
Cumberland Pharmaceuticals[20]	Children undergoing tonsillectomy	160	Multicentre, PL-controlled, 1 : 1 randomization	Post-operative fentanyl use	Currently enrolling

AUC-T° = area under the curve for temperature above 98.6°F (37.0°C) vs time; **IV-IB** = intravenous ibuprofen; **NJ** = New Jersey; **PL** = placebo; **pts** = patients; **tx** = treatment; ↓ indicates reduction.

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dose trended towards reduced morphine requirements and decreased VAS scores but did not reach statistical significance.[3]

The analgesic effects of intravenous ibuprofen were then confirmed in a multicentre placebo-controlled trial in adult women undergoing elective abdominal hysterectomy (table II).[4] In this study, 319 women who had undergone elective abdominal hysterectomy surgery were randomized to 800 mg intravenous ibuprofen or placebo, via a 30-minute infusion administered every 6 hours.[4] Compared with placebo, there was a significant reduction in the use of morphine through 24 hours in patients receiving 800 mg intravenous ibuprofen ($p < 0.001$).[4] In addition to the morphine-sparing effect, patients receiving 800 mg of intravenous ibuprofen also experienced a greater reduction in pain as measured by the VAS area under the curve for the first 24 hours after surgery ($p < 0.009$) and time to ambulation was also significantly shorter in the intravenous ibuprofen-treated patients compared with placebo (all $p < 0.01$).[4]

While the first two studies involved only post-operative dosing, a growing body of evidence suggests that pre-emptive multimodal analgesia, particularly with systemic NSAIDs, may provide even more prominent analgesia in the post-operative period.[21-24] Improved post-operative analgesia with pre-emptive analgesia may lead to shorter length of hospital stay and significant cost savings.[24] The mechanism believed to be responsible for the success of this approach is the prevention of the establishment of central sensitization.[21] Central sensitization is evoked by peripheral tissue injury (e.g. the surgical procedure) at the level of spinal neurons, manifesting in increased post-operative pain hypersensitivity and decreased pain threshold.[21] Systemic NSAIDs and opioids, among other agents and routes of administration, are believed to have synergistic and/or additive effects to attenuate this hypersensitivity and thereby improve analgesia.[21] The timing of prevention of central sensitization is critical as, once central sensitization has occurred, it takes significantly higher doses of analgesics to achieve similar levels of analgesia.[21]

The potential benefits of pre-operative dosing of intravenous ibuprofen for post-operative analgesia were assessed in a multicentre placebo-controlled study in adults undergoing orthopaedic surgery.[5] In this pain and morphine-sparing study, 185 adult patients set to undergo orthopaedic surgery were randomized to 800 mg intravenous ibuprofen or placebo, via 30-minute infusion administered prior to surgery and every 6 hours thereafter.[5] Compared with placebo, there was a significant reduction in pain with movement and at rest as measured by the VAS and verbal response scale (VRS) area under the curve for the 6- to 24-hour time period in patients receiving intravenous ibuprofen ($p < 0.001$).[5] Pre-operative dosing also allowed for measurement of immediate post-operative pain, and pain was significantly reduced at this time-point for intravenous ibuprofen-treated patients when compared with patients who received placebo ($p < 0.05$).[5] Intravenous ibuprofen-treated patients also used significantly less morphine (31%) than those patients treated with placebo ($p < 0.001$).[5] These data further confirm the analgesic efficacy of intravenous ibuprofen and provide evidence of the possible added benefits of pre-emptive administration in a multimodal analgesia surgical setting.

An additional study assessed pain in traumatic burn injury patients, but, since a majority of patients were unable to perform self-assessments of pain due to sedation or coma, there were not enough patients enrolled to show any statistical difference (table II).[9]

Taken together, these studies demonstrate the analgesic efficacy of a 30-minute infusion of intravenous ibuprofen in adult patients. Additional future pain studies should focus on the safety and efficacy of a rapid (5- to 10-minute) infusion of intravenous ibuprofen in adult patients, as well as on the pre-operative use of intravenous ibuprofen and intravenous ibuprofen for the treatment of pain in paediatric patients.

3.2 Fever

Intravenous ibuprofen was first studied as an experimental formulation by Bernard et al.,[2] in the Ibuprofen in Sepsis Study Group (table III). These investigators found that, while intravenous ibuprofen did not reduce mortality rates in sepsis

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Table III. Pharmacodynamic studies of intravenous-ibuprofen for reduction of fever

Study, year of publication	Pt type	n	Design	Primary endpoint	Conclusion
Bernard et al.,[2] 1997	Adult sepsis	455	Multicentre, PL-controlled, 1 : 1 randomization	Mortality	IV-IB did not ↓ mortality but did significantly ↓ body temperature
Morris et al.,[6] 2010	Febrile adults	120	Multicentre, PL-controlled, 1 : 1 randomization	Number of pts with a temperature <101°F after 4 h	IV-IB significantly ↓ the number of pts with a temperature <101°F after 4 h vs PL
Krudsood et al.,[7] 2010	Adult malaria	60	Single-centre, PL-controlled, 1 : 1 randomization	AUC-T° over the first 24 h of tx	IV-IB significantly ↓ AUC-T° for 0–24 h
Promes et al.,[9] 2011	Adult thermal burn	61	Multicentre, PL-controlled, 2 : 1 randomization	AUC-T° over the first 24 h of tx	IV-IB significantly reduced AUC-T° for 0–24 h
Cumberland Pharmaceuticals[25]	Febrile children	200	Multicentre, active comparator (acetaminophen), 1 : 1 randomization	Fever ↓ in first 2 h of tx	Currently enrolling
Cumberland Pharmaceuticals[15]	Adult pain or fever	150	Multicentre, open-label surveillance trial	Safety of a single dose of IV-IB administered over 5–10 min	Currently enrolling

AUC-T° = area under the curve for temperature above 98.6°F (37.0°C) vs time; **IV-IB** = intravenous ibuprofen; **PL** = placebo; **pt(s)** = patient(s); **tx** = treatment; ↓ indicates reduced.

patients, it did significantly reduce fever, tachycardia, oxygen consumption and lactic acidosis at a maximum dose of 800 mg four times per day.[2] Cumberland Pharmaceuticals Inc. then went on to conduct three additional studies involving intravenous ibuprofen in patients with fever of varying aetiology.[6,7,9]

The first of the fever trials was a multicentre, placebo-controlled, dose-ranging trial in hospitalized adult patients with fever due to varying underlying illnesses of a range of severity (table III).[6] In this study, 120 patients who had temperatures of 101°F or greater were randomized to receive intravenous ibuprofen 100 mg, 200 mg, 400 mg or placebo, via 30-minute infusions administered every 4 hours for 24 hours of treatment.[6] All intravenous ibuprofen dose levels resulted in a statistically significant ($p < 0.05$) reduction in the number of patients with a temperature less than 101°F after 4 hours, compared with placebo.[6] In addition, the difference in the mean temperature decrease from baseline was 1.00–1.38°F (95% CI −4.39, 7.13) for the intravenous ibuprofen-treated patients, compared with placebo.[6] Although this study was not designed to show statistically significant differences between intravenous ibuprofen dose levels, a clear dose response trend was observed, with the 400 mg dose having the greatest response.[6] Lastly, the first temperature measurement occurred 30 minutes following the completion of the 30-minute infusion of intravenous ibuprofen and revealed a significant temperature reduction, demonstrating a maximum 30-minute time of onset of the antipyretic effect of intravenous ibuprofen.[6]

The second fever trial was a single-centre placebo-controlled study in hospitalized malaria patients (table III).[7] In this study, 60 patients with uncomplicated *Plasmodium falciparum* malaria with temperatures ≥100.4°F were randomized to receive 400 mg of intravenous ibuprofen or placebo, via 30-minute infusions administered every 6 hours for 72 hours of treatment.[7] There was a statistically significant reduction in the area under the curve for temperature above 98.6°F (37.0°C) versus time (AUC-T°), as AUC-T° for intravenous ibuprofen compared with placebo measured over 0–4 hours, 0–24 hours and 0–72 hours were all significantly lower ($p < 0.05$).[7]

While the first two fever trials focused on patients with infectious diseases, the third fever trial was a multicentre placebo-controlled study in hospitalized burn patients (table III).[9] Traumatic burn injury leaves patients in a hypermetabolic

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state, leading to elevated body temperature.[9] In this multicentre placebo-controlled study, 61 patients with second- and/or third-degree thermal burns covering >10% total body surface area were randomly assigned in a 2 : 1 ratio to receive either 800 mg intravenous ibuprofen or placebo, via 30-minute infusions administered every 6 hours for 120 hours.[9] After 24 hours of dosing, there was a significant reduction in temperature in patients who received intravenous ibuprofen compared with those who received placebo ($p < 0.05$), and a trend in reduced temperature existed over the entire 120-hour dosing period in the patients who received intravenous ibuprofen compared with those who received placebo.[9]

Taken together, these studies demonstrate the antipyretic efficacy of a 30-minute infusion of intravenous ibuprofen in adult patients. Additional future fever studies should focus on the safety and efficacy of a rapid (5- to 10-minute) infusion of intravenous ibuprofen in adult patients, as well as on intravenous ibuprofen in febrile paediatric patients.

4. Clinical Impact of Rapid Infusion of Intravenous Ibuprofen

Although no studies have been conducted on the time of onset of analgesia of intravenous ibuprofen, some insight can be gleaned from studies on oral formulations of ibuprofen. Early studies of oral ibuprofen found a correlation between blood levels of ibuprofen and pain relief.[26] A more recent study in adult patients with post-operative dental pain found that the time of onset of pain relief following a dose of a commercially available ibuprofen oral Advil® Liqui-Gel preparation was 24.2 minutes.[27] An additional study using the same ibuprofen preparation in patients with headache found a time of onset of pain relief of 39 minutes.[28] Another group used an experimental formulation of ibuprofen in patients with post-operative dental pain and found the time of onset of pain relief to be 17–18.5 minutes.[29] Some studies have assessed plasma ibuprofen levels at these early timepoints and suggest that a level of 5–10 μg/mL is sufficient for the onset of pain relief.[30,31] However, the maximum analgesic effect of oral ibuprofen has been shown to be delayed compared with t_{max} by up to 2 hours.[32] The rapid (5- to 7-minute) infusion of intravenous ibuprofen had a 50% higher C_{max} than longer infusions and 100% higher C_{max} than oral ibuprofen (figure 1a). The C_{max} level may also be critical for optimal analgesia, but the effect of a rapidly achieved supra-C_{max} has never been studied.

Overall, a rapid infusion of intravenous ibuprofen would (i) allow for a significant shortening of t_{max}; (ii) eliminate any variability in efficacy associated with variable absorption from the gastrointestinal tract of orally administered ibuprofen; and (iii) provide a more rapid and reliable time of onset of analgesia than orally administered ibuprofen or the 30- to 60-minute intravenous infusion protocol. These improvements garnered by the rapid infusion of intravenous ibuprofen are particularly critical in the peri-operative setting, where time and pain are closely related. However, rapid infusion of intravenous ibuprofen may also prove beneficial to patients presenting with acute injuries in the emergency department.

Similar time-of-onset studies have been completed for oral ibuprofen in fever, and the fever studies also included t_{max} assessments. These studies found a time of onset of antipyresis of 1–1.5 hours, while t_{max} was reached in 40–60 minutes.[30,31] Similar to analgesic use, the maximum antipyretic effect of oral ibuprofen has been shown to be delayed compared to t_{max} by up to 2 hours.[33] The time of onset of antipyretic effect for intravenous ibuprofen was evaluated by Morris et al.[6] in the intravenous ibuprofen fever study that also collected pharmacokinetic data. The authors found a time of onset of antipyresis for intravenous ibuprofen at the first measurement of temperature after the 30-minute infusion (30 minutes after the end of infusion).[6] For its antipyretic effect, ibuprofen must cross the blood brain barrier and reach the thermoregulatory centre of the hypothalamus and this movement and activity of ibuprofen likely relies on the level of C_{max}.[34] The rapid infusion of intravenous ibuprofen had a 50% higher C_{max} than longer infusions and 100% higher than oral ibuprofen (figure 1b).

Just as for analgesic efficacy, a rapid infusion of intravenous ibuprofen would (i) provide a significant shortening in t_{max}; (ii) eliminate any

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variability in efficacy associated with variable absorption from the gastrointestinal tract of orally administered ibuprofen; and (iii) provide a more rapid and reliable time of onset of antipyresis than orally administered ibuprofen or the 30–60 minute intravenous infusion protocol. Even with the noted 30-minute delay to time of antipyretic effect, this rapid infusion of intravenous ibuprofen could provide meaningful fever reduction to critically ill patients in as little as 35 minutes, a significant improvement over the 1–1.5 hours for orally administered ibuprofen or the 30–60 minute intravenous infusion protocol.

5. Future Directions

While future pain and fever studies focusing on the safety and efficacy of a rapid infusion of intravenous ibuprofen in adult and paediatric patients are needed, a number of additional studies are already underway. Three single-centre pain studies are currently underway in adult patients undergoing inguinal hernia repair[17] or electroconvulsive therapy[18] and those requiring treatment for migraine headache[19] (table II). The first pain study in children utilizing a tonsillectomy model[20] is also underway (table II) as is the first fever study in children[25] (table III). Two safety surveillance trials[15,16] utilizing the rapid infusion with pain and fever endpoints are also underway (tables II and III).

6. Conclusion

NSAIDs have risks, including gastrointestinal, renal, cardiovascular and bleeding risks.[35] Since NSAIDs exact their analgesic, anti-inflammatory and antipyretic activity through the direct binding and inhibition of cyclo-oxygenase (COX) enzymes, differences in COX isoform affinity lead to significant differences in safety profiles among NSAIDs.[35] These risks are typically associated with long-term use, but the acute inhibition of COX enzymes may also play a role.[35] Individual NSAIDs have somewhat different safety profiles due to the way in which they differ in their degree of COX-1 versus COX-2 inhibitory activity and thus may differ in their safety profiles.[36] An NSAID that inhibits COX-1 to a greater degree than COX-2 may have greater risk pertaining to renal, cardiovascular and bleeding-related adverse events.[36] An NSAID that inhibits COX-2 to a greater degree than COX-1 may have greater risk pertaining to cardiovascular events.[36] An NSAID with a more balanced COX-1 to COX-2 inhibition ratio, such as ibuprofen, may provide a better safety profile.[36]

Overall, intravenous ibuprofen presents an effective therapy for the treatment of pain and fever, with a strong safety profile. In addition, the rapid infusion of intravenous ibuprofen provides a significant improvement in the delivery of a beneficial therapy and will help improve patient care in the field of multimodal pre-emptive analgesia, as well as emergency and critical care.

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