Pharmacokinetics, safety, and tolerability of a rapid infusion of i.v. ibuprofen in healthy adults

LEO PAVLIV, BRYAN VOSS, AND AMY ROCK

Purpose. The pharmacokinetics, safety, and tolerability of a rapid infusion of i.v. ibuprofen in healthy adults were evaluated.

Methods. In this randomized, double-blind, placebo-controlled, single-dose, crossover study, 12 healthy subjects aged 18–65 years were randomized to receive a single dose of either 800 mg i.v. ibuprofen (infused over five to seven minutes) concomitantly with an oral placebo or 800 mg oral ibuprofen with concomitant i.v. placebo (0.9% sodium chloride injection). After a six-day washout period, subjects received the treatment not previously received. Blood samples were taken 1 hour before each dose of study medication was administered and throughout the 12 hours thereafter. Plasma ibuprofen concentrations were determined using validated liquid chromatography–tandem mass spectrometry methods. The frequency and severity of treatment-emergent adverse effects were monitored throughout the study.

Results. The maximum plasma concentration (C\text{max}) of i.v. ibuprofen was approximately twice that of oral ibuprofen, and the (t\text{max}) of i.v. ibuprofen was 0.11 hour, compared with 1.5 hours for oral ibuprofen. However, the elimination half-life of i.v. and oral ibuprofen did not differ, both of which were approximately 2 hours. Oral ibuprofen was 100% bioavailable; therefore, the area under the concentration–time curve did not differ between i.v. and oral ibuprofen. In addition, i.v. ibuprofen infused over five to seven minutes did not differ in terms of safety or tolerability when compared with oral ibuprofen.

Conclusion. I.V. ibuprofen, when administered over five to seven minutes in healthy subjects, achieved a higher C\text{max} and a more rapid t\text{max} than did oral ibuprofen and was found to be safe and well tolerated.

Index terms: Antiinflammatory agents; Blood levels; Chromatography, liquid; Drug administration routes; Drugs, availability; Excretion; Half-life; Ibuprofen; Injections; Pharmacokinetics; Spectrometry, mass; Toxicity

Am J Health-Syst Pharm. 2011; 68:47-51

Pain and fever are clinical conditions that demand timely and effective treatment to achieve and maintain patient comfort and a good clinical outcome.\textsuperscript{1,3} Traditional oral analgesics and antipyretics have a relatively slow onset of action or clinical effect attributable to the time required to absorb the medication from the gastrointestinal tract. In addition, many hospitalized patients may not be able to take oral medications due to intubation, emesis, reduced gastrointestinal motility or function, or the effects of anesthesia and sedation, further necessitating the need for intravenous analgesics and antipyretics.\textsuperscript{1,4,5}

Inadequate acute pain management has substantial consequences for patients, including delayed ambulation, shortened or missed rehabilitation sessions, decreased quality of life, increased cost of care, and the potential for progression from acute to chronic pain.\textsuperscript{6,9} The World Health Organization (WHO) recommends a multimodal approach to the treatment of pain, with nonopioid analgesics recommended as first-line treatment for pain and as adjuncts to opioids for moderate-to-severe pain.\textsuperscript{10} A large meta-analysis of randomized, double-blind studies found that multimodal analgesic therapy with nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase-2-selective NSAIDs, and acetaminophen significantly decreased morphine dosage requirements (by 13–55%), postoperative nausea (by 12%), vomiting (by 32%), nausea and vomiting (by 30%), and sedation scores (by 29%).\textsuperscript{11,12}

Leo Pavliv, B.S.,Pharm., is Senior Vice President, Operations; Bryan Voss, Ph.D., is Research Associate; and Amy Rock, Ph.D., is Senior Director, Regulatory and Scientific Affairs, Cumberland Pharmaceuticals, Nashville, TN.

Address correspondence to Mr. Pavliv at Cumberland Pharmaceuticals, 2525 West End Avenue, Suite 950, Nashville, TN 37203 (lpavliv@cumberlandpharma.com).

Funded in full by Cumberland Pharmaceuticals.

Mr. Pavliv and Drs. Voss and Rock are employees of Cumberland Pharmaceuticals Inc., which manufactures the Caldolor brand of i.v. ibuprofen.

Copyright © 2011, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/11/0101-0047/$9.00. DOI 10.2146/ajhp100120
Early clinical trials of i.v. ibuprofen found the drug to be both safe and efficacious for the treatment of pain and fever when administered over 30–60 minutes. However, a shorter infusion time could further expedite i.v. ibuprofen's onset of effect. Anesthetologists may use NSAIDs before and after a surgical procedure to lessen pain after surgery and to decrease the amount of opioid pain medication required. A shorter infusion time for i.v. ibuprofen would be of significant value in this setting as it would hasten the onset of action before surgery, providing preemptive analgesia, and after surgery, providing continued opioid-sparing and antinflammatory analgesia. Further, a shorter infusion time would decrease the time spent administering the drug, allowing for more efficient use of clinical time. I.V. ibuprofen for the treatment of fever, particularly high fever, would be of value for patients unable to tolerate oral antipyretics, and a shorter infusion could decrease the onset of action for temperature reduction. In addition, research suggests a positive correlation between blood levels of ibuprofen and pain relief, meaning that a more rapid infusion of i.v. ibuprofen may reduce pain more quickly.

We studied the safety and pharmacokinetics of i.v. ibuprofen administered over five to seven minutes.

Methods

This randomized, double-blind, placebo-controlled, single-dose, crossover study was conducted from March to April 2009 at a single site in Australia (CPR Pharma Services Pty Ltd, Underdale, South Australia), which specializes in early-phase clinical studies. An independent human research ethics committee from the University of South Australia approved the study, and potential study participants were screened for eligibility by CPR Pharma Services study personnel.

Healthy volunteers age 18–65 years were eligible for study participation but were excluded if they lacked good venous access in both arms, had a history of allergy or hypersensitivity to NSAIDs or any component of i.v. ibuprofen, had never taken aspirin or ibuprofen, had a history of alcohol or drug abuse in the two months before study drug administration, used prescription drugs (not including oral contraceptives) within 14 days before study drug administration, used aspirin within 7 days before study drug administration, used nonprescription pain relievers (NSAIDs or acetaminophen) within 3 days before study drug administration, used investigational drugs or donated blood or blood products within 30 days before administration of study medication, or had a calculated creatinine clearance of <75 mL/min (estimated using the Cockcroft-Gault equation). Additional exclusion criteria were the presence or history of asthma, bleeding tendency, breast cancer, hypertension, heart failure, peptic ulcer disease, inflammatory bowel disease or any other gastrointestinal disorder, and renal or hepatic disease. Pregnant or nursing women and any subject with a clinically significant laboratory test value were also excluded. Participants received $590 Australian (approximately $535 U.S.) for study participation.

Consent was provided by all study participants. Subjects were randomized in a 1:1 ratio (treatment assignment was blinded) to receive a single dose of either 800 mg i.v. ibuprofen infused over five to seven minutes concomitantly with an oral placebo or 800 mg oral ibuprofen with concomitant i.v. placebo (0.9% sodium chloride injection). The randomization scheme was prepared by a nonblinded statistician (not involved in study conduct) and provided to a nonblinded pharmacist at the study site. After a 12-day screening period, a blood sample was taken from each subject for pharmacokinetic analysis one hour prior before receiving the first dose of study medication. Subjects were required to swallow the oral dose within the first minute of the i.v. infusion. Blood samples for pharmacokinetic analysis were then taken throughout the 12 hours after this dose. This treatment period was followed by a 6-day washout period. After washout, a blood sample was taken and then subjects received a single dose of the study medication that they had not already received. Blood samples for pharmacokinetic analysis were taken throughout the 12 hours after this dose.

Study medication was provided as follows: (1) 8 mL i.v. ibuprofen 100 mg/mL added to a 250-mL bag of 0.9% sodium chloride injection that had 58 mL removed from it immediately before adding the 8 mL i.v. ibuprofen (final bag volume 200 mL, including i.v. ibuprofen), along with placebo capsule, and (2) 800-mg tablet of ibuprofen, along with 200 mL of 0.9% sodium chloride injection.

The active oral drug (800 mg ibuprofen) was a white tablet. The oral placebo was a size-00 capsule filled with lactose. To maintain the blinding of patients, each dose was administered in an opaque container. The contents of the container were unknown to blinded staff and participants. At the time of administration, the contents were tipped into the mouth of the participant by unblinded staff members to avoid identification of the ibuprofen form. The subject was told to swallow the drug immediately and not to discuss the consistency or taste of the drug. The i.v. doses of study medication were prepared as blinded material for the participant by a registered nurse.

Pharmacokinetic analysis. The primary objective of this study was to evaluate the pharmacokinetic profile of a single dose of i.v. ibuprofen administered over 5–7 minutes. Plasma ibuprofen concentrations were determined using validated liq-
uid chromatography-tandem mass spectrometry methods (Analytical laboratory method I-005/1). Determination of ibuprofen in human plasma by high-performance liquid chromatography using liquid/liquid extraction. CMAX Pty. Ltd.). Blood samples for pharmacokinetic analyses were collected at the following time points in each treatment period: before dose administration; immediately after completion of the i.v. infusion; and 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after dose administration.

Safety analysis. The secondary objective of this study was to evaluate the safety and tolerability of a single dose of i.v. ibuprofen administered as a rapid infusion compared with a dose of oral ibuprofen. The occurrence and severity of treatment-emergent adverse effects (i.e., any event not present before the initiation of the study treatment) were monitored throughout the study. A serious adverse event was defined as any event that was life-threatening, required hospitalization, or resulted in persistent or significant disability, incapacity, or death. The tolerability of the rapid-infusion protocol was assessed based on the occurrence and severity of adverse effects near the infusion site, as previous studies have demonstrated the safety and tolerability of longer duration infusions of i.v. ibuprofen.13,14

Statistical analysis. Pharmacokinetic parameters of ibuprofen were tabulated and plotted for each subject and summarized using descriptive statistics.

The maximum plasma drug concentration (C\text{max}), area under the plasma concentration-time curve (AUC\text{0-12 h}), and AUC\text{0-12 h} for oral and i.v. dose forms were determined and summarized by geometric mean and 90% confidence interval (CI), calculated as the back-transformation of the mean and confidence limits of logarithmic-transformed parameters.

Adverse-effect data were listed individually and summarized by body system organ class and preferred terms within system organ class. These events were coded using The Medical Dictionary for Regulatory Activities.21,22 The treatment groups were compared with respect to the number of participants reporting adverse effects overall and within body systems, unadjusted using the chi-square test and adjusted for center by using the Cochran-Mantel-Haenszel test.

SAS software, version 9.1 (SAS Institute, Cary, NC), was used to prepare the data listings, calculate descriptive statistics for summary tables, and conduct statistical tests. The a priori level of significance was 0.05.

Results

Subject characteristics. In this crossover study, the 12 subjects (9 men, 3 women) enrolled were Caucasian and had a mean ± S.D. age of 31.7 ± 10.8 years, a mean ± S.D. height of 177.9 ± 6.8 cm, and a mean ± S.D. weight of 76.9 ± 12.4 kg. Pharmacokinetics. Figure 1 shows the plasma concentration-time curve for an 800-mg i.v. ibuprofen dose infused over 5–7 minutes compared with 800 mg of oral ibuprofen. These data are summarized in Table 1. The C\text{max} of the i.v. ibuprofen infusion was approximately twice that of oral ibuprofen, and the time to the maximum plasma concentration (t\text{max}) of i.v. ibuprofen was 0.11 hr (6.5 minutes) (end of the infusion), compared with 1.5 hours for oral ibuprofen. However, the elimination half-life (t\text{1/2}) of i.v. and oral ibuprofen did not differ significantly, both of which were approximately 2 hours. Lastly, oral ibuprofen was essentially 100% bioavailable compared with i.v. ibuprofen (mean ratio of geometric least-squares mean of AUC\text{0-12 h}, 90% CI, 89.6–111.6%).

Safety. Treatment-emergent adverse effects were reported for 6 of the 12 subjects. Of these, 4 occurred with i.v. ibuprofen and 2 with oral ibuprofen (p = 0.355). These events were of mild intensity and included infusion-site pain (i.v. ibuprofen) and hematoma and epistaxis (oral ibuprofen). No subjects suffered a serious adverse event, and there were no deaths.

Discussion

Rapid pain control and fever resolution are important factors for determining patient comfort level and play a critical role in patient outcome.13 In general, oral medications may have a latency to clinical effect due to absorption time.23 In addition, oral medications can have inconsistent absorption in hospitalized patients.24 I.V. ibuprofen is effective in controlling pain as an adjunct to opioids and in resolving fever, and a rapid-infusion protocol allows for more convenient administration options without adding safety concerns.13,15

I.V. ibuprofen is the only i.v. antipyretic currently available in the United States and is currently one of two injectable NSAIDs available for the treatment of pain. Ketorolac is also available as an i.v. or intramuscular injection.23 I.V. ibuprofen must be diluted to a concentration of no less than 4 mg/mL before administration.15 However, ketorolac is not labeled for the treatment of fever, is contraindicated for preoperative administration, and is limited to a maximum duration of five days’ use.

I.V. ibuprofen 800 mg administered over five to seven minutes reaches a higher concentration in the plasma more quickly than an equivalent oral dose. While the increased C\text{max} and decreased t\text{max} of i.v. ibuprofen over the oral formulation seen in this study may lead to the assumption that i.v. ibuprofen has greater efficacy than its oral counterpart, this study neither addressed nor proved this hypothesis. This study did demonstrate that the rapid infusion of i.v. ibuprofen was well tolerated, as only
a few mild infusion site issues were reported.

This study had several limitations. No direct comparison was made with i.v. ibuprofen administered over 30 minutes. However, a 30-minute infusion protocol has been previously studied and did not show any safety or tolerability differences when compared with placebo. In addition, adverse gastrointestinal and renal effects were not directly measured in this study. However, adverse gastrointestinal effects are typically associated with long-term NSAID use, and neither gastrointestinal nor renal adverse effects have been demonstrated in previous studies of i.v. ibuprofen. Since this study was completed in a small cohort of healthy subjects, rapid infusion of i.v. ibuprofen could affect critically ill and postoperative patients differently, but that is unlikely, considering that 30–60-minute infusions of i.v. ibuprofen have been found to be both safe and effective in these patient populations.

**Conclusion**

I.V. ibuprofen, when administered over five to seven minutes in healthy subjects, achieved a higher $C_{\text{max}}$ and a more-rapid $t_{\text{max}}$ than did oral ibuprofen and was found to be safe and well tolerated.