Clin Drug Investig (2016) 36:1051–1058
DOI 10.1007/s40261-016-0453-4

ORIGINAL RESEARCH ARTICLE

Pharmacokinetic Properties of Intravenous Ibuprofen in Healthy Chinese Volunteers

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Published online: 23 August 2016

Abstract

Background and Objectives No pharmacokinetic data of intravenous ibuprofen were available in a Chinese population and the published information remained inadequate. The present study aimed to investigate the pharmacokinetic properties of intravenous ibuprofen in healthy Chinese volunteers after single- and multiple-dose administration.

Methods Twelve subjects received single doses of 200, 400, and 800 mg intravenous ibuprofen, respectively, and multiple doses of 400 mg intravenous ibuprofen, four times per day (every 6 h) till the morning of the sixth day in each study period.

Results After single doses of 200, 400 and 800 mg and multiple doses of 400 mg intravenous ibuprofen, the main pharmacokinetic parameters obtained were: maximum plasma concentration (C_{max}) 23.05 ± 2.96, 41.90 ± 3.22, 76.06 ± 8.70, and 49.53 ± 3.92 μg/ml, respectively, which were achieved immediately at the end of the infusion; area under the plasma concentration–time curve from time zero to the time of last quantifiable concentration (AUC_{0-t}) 49.82 ± 10.92, 88.79 ± 12.43, 152.34 ± 25.23, and 106.68 ± 18.94 μg·h/mL, respectively; AUC from time zero to infinity ($AUC_{0-\infty}$) 51.91 ± 10.67, 91.46 ± 12.06, 155.04 ± 25.70, and 108.58 ± 19.49 μg·h/ml, respectively; half-life ($t_{½}$) 1.87 ± 0.30, 1.93 ± 0.24, 2.02 ± 0.38, and 1.74 ± 0.26 h, respectively. The accumulation index (AI) was 1.22 ± 0.17 after multiple doses. The most obvious accumulation was observed in males; other parameters revealed no significant differences.

Conclusions Similar pharmacokinetic properties of intravenous ibuprofen in healthy Chinese volunteers were observed to those reported in a Caucasian population. Multiple doses of intravenous ibuprofen every 6 h caused slight accumulation. Except for the AI, sex did not affect the pharmacokinetics of intravenous ibuprofen.

Chictr.org identifier ChiCTR-IIR-15007347.

Key Points

The pharmacokinetic profile of intravenous ibuprofen in healthy Chinese subjects is similar to that of a Caucasian population.

Multiple doses of intravenous ibuprofen caused slight accumulation.

Sex did not affect the pharmacokinetics of intravenous ibuprofen except for the AI.

1 Introduction

Ibuprofen, which is (±)-2-(p-isobutylphenyl) propionic acid, is one of the most frequently used non-steroidal anti-inflammatory drugs (NSAIDs) [1, 2]. Ibuprofen has analgesic, anti-inflammatory, and antipyretic properties. Like that of other NSAIDs, the mechanism of action of ibuprofen involves inhibition of cyclooxygenase (COX-1 and COX-2) to decrease the conversion of arachidonic acid into thromboxane and prostacyclin [3, 4].

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The oral form of ibuprofen has been marketed for decades. However, in clinical practice, many hospitalized patients are frequently unable to ingest or tolerate oral NSAIDs. To address this unmet medical need, the US Food and Drug Administration (FDA) approved intravenous ibuprofen in 2009 [5–7]. Intravenous ibuprofen is an NSAID indicated for the management of mild to moderate pain, the management of moderate to severe pain as an adjunct to opioid analgesics, and the reduction of fever [3, 5, 8]. The approved dosage is 400–800 mg intravenously over 30 min every 6 h as necessary for management of pain and 400 mg intravenously over 30 min, followed by 400 mg every 4–6 h as necessary for management of fever [8].

Although the pharmacokinetic characteristics of intravenous ibuprofen have been reported previously [3, 9], no pharmacokinetic data of intravenous ibuprofen were available in a Chinese population and to date intravenous ibuprofen has not been approved in China. In the previously reported studies in Caucasian populations, a range of dosing levels and infusion times have been utilized to evaluate the pharmacokinetic properties of intravenous ibuprofen, which included: single 60-min infusion of 400 and 800 mg; single 30-min infusion of 100, 200, and 400 mg; single rapid infusion (5–7 min) of 800 mg [8, 10, 11]. Further data about intravenous ibuprofen are needed to define its pharmacokinetic characteristics in multiple doses and the effect of gender on its pharmacokinetics should be included. The present study aimed to investigate the pharmacokinetic properties of intravenous ibuprofen in healthy Chinese volunteers after single- and multiple-dose administration. This was a registered study approved by the China Food and Drug Administration (Registration number 2014L01894).

2 Subjects and Methods

2.1 Study Design

This was an open-label, randomized, single- and multiple-dose study which set out to enroll 12 (six male and six female) healthy Chinese volunteers. The whole study included single- and multiple-dose stages. In the single-doses stage, a randomized, three-way crossover design was conducted. Twelve subjects were allocated in a 1:1:1 ratio to receive a single dose of 200, 400, or 800 mg intravenous ibuprofen in randomized sequence based on a computer-generated table of random numbers. In the subsequent multiple-dose stage, the same 12 subjects received multiple doses of 400 mg intravenous ibuprofen, four times per day (every 6 h) until the morning of the sixth day. The washout between each period was 1 week. The study flowchart is shown in Fig. 1.

2.2 Subjects

Healthy male and female Chinese volunteers aged 18–40 years and with a body mass index between 19 and 24 kg/m^2 were eligible for recruitment. Other inclusion criteria included a healthy status confirmed by medical history, physical examination, 12-lead ECG, and laboratory tests (hematology, blood biochemistry, urinalysis, hepatitis B surface antigen, HIV antibody, tests for alcohol and other drugs of abuse) and nonsmoking status. Subjects with any allergic history or history of cardiac, pulmonary, renal, hepatic, gastrointestinal, or hematologic abnormality or any other acute or chronic disease were excluded. Additional exclusion criteria included pregnant or nursing women and exposure to any investigational medication within 30 days.

2.3 Drug Administration and Sampling

The study intravenous ibuprofen (400 mg/4 ml, 800 mg/8 ml; batch number 1014052, 1014021) was manufactured by Beijing Alica Pharmaceutical Sci-Tech Co. Ltd. (Beijing, People's Republic of China).

In the single-dose stage, the subjects received a single dose of 200, 400, or 800 mg intravenous ibuprofen at 7:00 am on each dosing day. In the multiple-dose stage, the subjects received multiple doses of 400 mg intravenous ibuprofen, four times per day (every 6 h: 7:00 am, 1:00 pm, 7:00 pm, and 1:00 am) until 7:00 am of the sixth day (total 21 times). The study intravenous ibuprofen was administered in a 200-ml bag of normal saline. The infusion time of each dosing was 30 min and the speed of infusion was controlled by an infusion pump (type 8712212, B.Braun Melsungen AG, Hessen, Germany).

Blood samples ($\sim$3.5 ml) were collected from the vein in the arm opposite to that used for infusion before and at 10, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h after the start of infusion in each single-dose stage and the last dosing of the multiple-dose stage. In the multiple-dose stage, additional predose samples were collected to check the trough level at 7:00 am on the fourth day, 7:00 am, 1:00 pm, 7:00 pm on the fifth day, and 1:00 am and 7:00 am on the sixth day.

2.4 Tolerability Assessment

The subjects were under continuous medical supervision in the Phase I Unit of West China Hospital, Sichuan University during the study. Tolerability was evaluated by

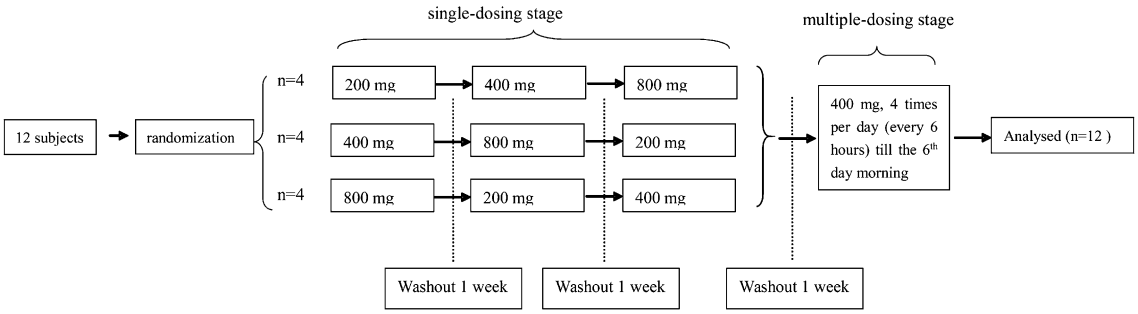

Fig. 1 Flowchart of the study

monitoring adverse events, physical examinations, 12-lead ECG, and laboratory tests (hematology, blood biochemistry, and urinalysis). An adverse event was considered an untoward medical event in a subject during the study and which did not necessarily have a causal relationship with the treatment. Adverse events were classified as mild, moderate, or severe. ECG and laboratory tests were conducted at the screening period and at the end of the study. All the laboratory tests were performed in the clinical laboratory of West China Hospital, Sichuan University, which was authenticated by College of American Pathologists (CAP).

2.5 Assays of Ibuprofen

Plasma ibuprofen was quantified by a high pressure liquid chromatography (HPLC) method developed and validated before sampling. Chromatography was performed using Shimadzu 2010 HPLC system (Shimadzu Corporation, Kyoto 604-8511, Japan) and the data was processed by Shimadzu Lab Solutions Analysis Data System. Separation was carried out on a SHISEIDO C18 column (100 mm × 4.6 mm, 5 μm, SHISEIDO Group, Tokyo 104-0061, Japan) maintained at 35 °C. The mobile phase consisted of methanol, water, and methanoic acid (75:25:0.1, v/v/v) and was delivered at a flow rate of 1 ml/min. After the protein plasma sample was precipitated with acetonitrile, the supernatant was injected into the column. The detection time was 5.8 min and the detection wavelength was 225 nm. Zaltoprofen was used as the internal standard (IS). The retention times for ibuprofen and IS were 4.7 and 3.7 min, respectively. Typical chromatograms are shown in Fig. 2. No interference from endogenous substances in plasma samples was observed at the retention time of ibuprofen and IS. The calibration curve of ibuprofen was linear over the range of 0.8–150 μg/ml. The lower limit of quantification (LOQ) in plasma was 0.8 μg/ml. The accuracy in LOQ was 102.79–109.65 %. The intra-day RSD was 3.92–11.52 % and inter-day RSD 9.28 %. Stability studies showed the analyte was stable under the following conditions: long-term stability (−40 °C for 300 days), freeze-thaw stability (5 freeze-thaw cycles from −80 °C to room temperature), at room temperature for 6 h and processed samples at 4 °C in the injection chamber for 20 h. All the assay validation results showed the method in the present study was qualified for the quantification of plasma ibuprofen.

2.6 Pharmacokinetics and Statistical Analysis

Time to maximum concentration (T_{max}) and maximum plasma concentration (C_{max}) of intravenous ibuprofen were obtained directly from the concentration–time data. Other pharmacokinetic parameters were calculated using WinNonlin Version 6.1 (Pharsight Corporation, Mountain View, CA, USA) with noncompartmental analysis method: Area under the plasma concentration–time curve (AUC) from time zero to the time of last quantifiable concentration (AUC_{0-t}) was calculated with the linear trapezoidal rule. AUC from time zero to infinity ($AUC_{0-\infty}$) was obtained as the sum of AUC_{0-t} and Ct/λ. Ct was the last measured concentration and λ was the slope of linear regression of the log-transformed concentration-time curve. Half-life ($t_{½}$) was calculated as 0.693/λ. The statistical analyses of pharmacokinetic parameters were performed using SPSS Version 18.0 (SPSS Inc. Chicago, IL, USA). The paired T test (normal distribution data) or paired nonparametric-tests (abnormal distribution data) were used to determine significant differences between single- and multiple-dose groups. Independent-samples T test (normal distribution data) or independent-samples nonparametric-tests (abnormal distribution data) were used to determine significant differences between male and female groups. For all the analyses, $P < 0.05$ was considered as statistically significant.

3 Results

3.1 Subjects

In total 12 healthy subjects (six male and six female) were enrolled and completed the study. The demographics of the subjects are presented in Table 1.

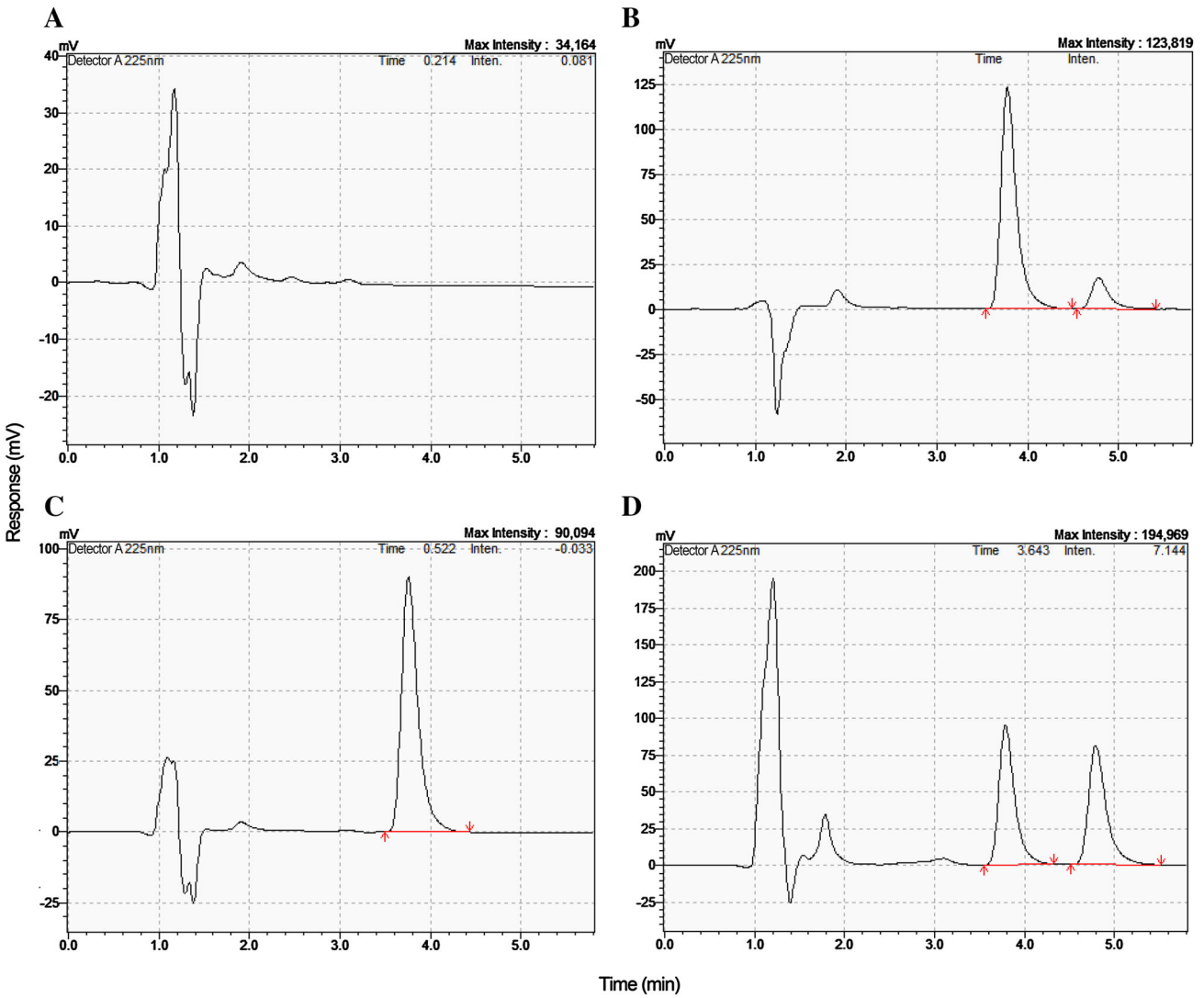

Fig. 2 High pressure liquid chromatography (HPLC) of ibuprofen assays: **a** blank plasma solution, **b** ibuprofen and reference standard solution, **c** blank plasma with reference standard solution, **d** subject plasma solution

Table 1 Demographics of the subjects

Demographic	Total (n = 12)	Male (n = 6)	Female (n = 6)
Age, years	23.6 ± 1.2	24.0 ± 1.5	23.2 ± 0.8
Weight, kg	57.8 ± 7.5	62.5 ± 6.7	53.0 ± 5.0
Height, cm	163.3 ± 5.2	166.7 ± 4.9	159.8 ± 2.9
Body mass index, kg/m^2	21.6 ± 1.6	22.4 ± 1.5	20.7 ± 1.3

All values are mean ± SD

3.2 Pharmacokinetic Properties

After single doses of 200, 400, and 800 mg and multiple doses of 400 mg of intravenous ibuprofen, the mean plasma ibuprofen concentration–time curves are shown in Fig. 3. The detailed pharmacokinetic parameters of intravenous ibuprofen are presented in Table 2.

In the multiple-dose period, the plasma ibuprofen accumulation was evaluated with the Accumulation Index (AI) calculated as $AUC_{ss}/AUC_{0-\tau,1}$ [12, 13]. AUC_{ss} was the area under curve of one dosing interval after steady-state; $AUC_{0-\tau,1}$ was the area under curve of one dosing interval after first dosing. The AI was 1.22 ± 0.17, which indicated slight accumulation after multiple doses of 400 mg of

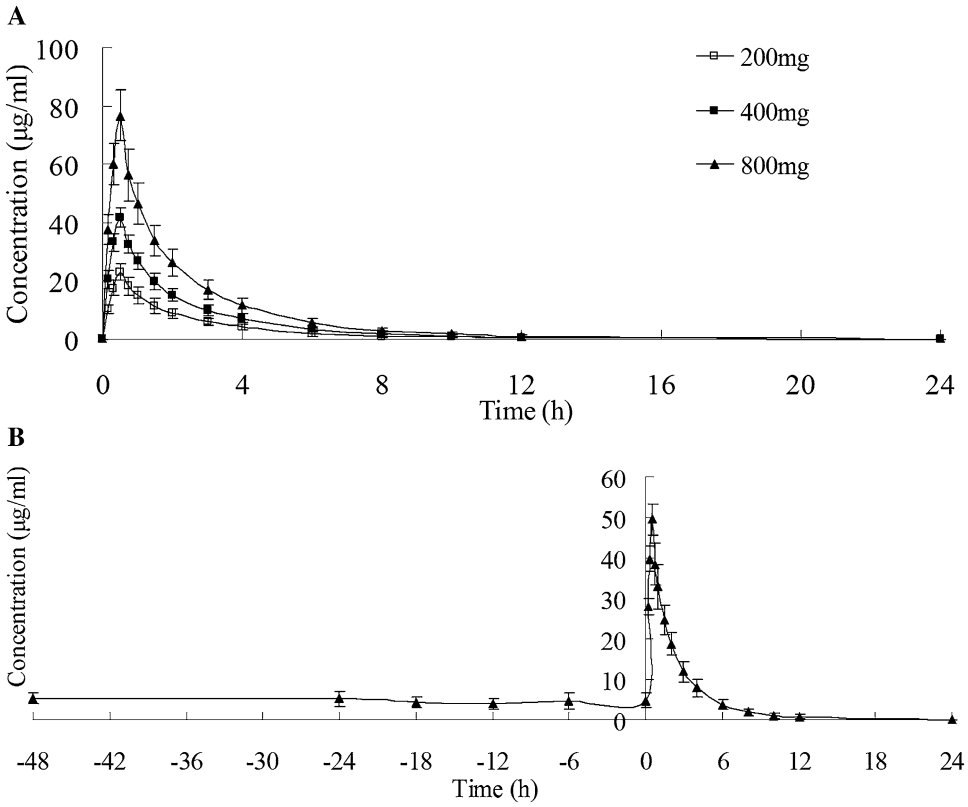

Fig. 3 Mean (SD) plasma concentration–time curves of intravenous ibuprofen after single doses of 200, 400, and 800 mg (**a**) and multiple doses of 400 mg (**b**)

Table 2 Pharmacokinetic parameters of intravenous ibuprofen in healthy Chinese volunteers (n = 12)

PK parameter	Single doses			Multiple doses
	200 mg	400 mg	800 mg	400 mg
T_{max}, h	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00
C_{max}, μg/ml	23.05 ± 2.96	41.90 ± 3.22	76.06 ± 8.70	49.53 ± 3.92
AUC_{0-t}, μg·h/mL	49.82 ± 10.92	88.79 ± 12.43	152.34 ± 25.23	106.68 ± 18.94
$AUC_{0-\infty}$, μg·h/mL	51.91 ± 10.67	91.46 ± 12.06	155.04 ± 25.70	108.58 ± 19.49
$t_{½}$, h	1.87 ± 0.30	1.93 ± 0.24	2.02 ± 0.38	1.74 ± 0.26
Vd, L	10.61 ± 1.96	12.29 ± 1.77	15.18 ± 2.71	9.06 ± 0.72
CL, L/h	3.97 ± 0.65	4.44 ± 0.57	5.29 ± 0.86	4.17 ± 0.60
C_{ss}, μg/ml	–	–	–	16.31 ± 2.46
C_{min}, μg/ml	–	–	–	3.62 ± 1.18
AUC_{ss}, μg·h/mL	–	–	–	97.89 ± 14.74
DF, %	–	–	–	285.73 ± 36.42
AI	–	–	–	1.22 ± 0.17

All values are mean ± SD

T_{max} time to maximum concentration, C_{max} maximum plasma concentration, AUC area under the plasma concentration–time curve, AUC_{0-t} AUC from time zero to the last quantifiabel concentration, $AUC_{0-\infty}$ AUC from time zero to infinity, $t_{½}$ half-life, CL clearance, Vd volume of distribution, C_{ss} steady-state plasma concentration, C_{min} minimum plasma concentration, DF degrees of fluctuation, AI Accumulation Index

intravenous ibuprofen every 6 h. Comparison of the pharmacokinetic parameters of single and multiple doses of 400 mg intravenous ibuprofen showed that C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for multiple doses increased more than those for single doses and the differences were statistically significant ($P < 0.05$), which also indicated the accumulation after multiple doses.

Table 3 shows the comparison of the main pharmacokinetic parameters between male and female subjects. The AI values were significantly different (male: 1.32 ±

Table 3 Comparison of pharmacokinetic parameters of intravenous ibuprofen in male and female subjects

PK parameter	Single doses						Multiple doses	
	200 mg		400 mg		800 mg		400 mg	
	Male (n = 6)	Female (n = 6)	Male (n = 6)	Female (n = 6)	Male (n = 6)	Female (n = 6)	Male (n = 6)	Female (n = 6)
T_{max}, h	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00	0.50 ± 0.00
C_{max}, μg/ml	22.41 ± 2.69	23.69 ± 3.33	41.06 ± 3.47	42.75 ± 3.00	74.08 ± 8.08	77.70 ± 9.59	51.33 ± 2.64	47.74 ± 4.37
AUC_{0-t}, μg·h/mL	51.05 ± 14.52	48.58 ± 6.93	88.59 ± 16.71	88.99 ± 7.79	149.49 ± 18.51	154.71 ± 31.36	115.47 ± 20.55	97.90 ± 13.47
$AUC_{0-\infty}$, μg·h/mL	53.24 ± 14.17	50.58 ± 6.75	91.64 ± 15.94	91.28 ± 8.10	151.84 ± 18.12	157.71 ± 32.25	117.50 ± 21.38	99.66 ± 13.69
$t_{½}$, h	1.93 ± 0.28	1.81 ± 0.34	1.94 ± 0.29	1.92 ± 0.22	1.94 ± 0.18	2.08 ± 0.50	1.83 ± 0.34	1.65 ± 0.12
Vd, L	10.82 ± 2.03	10.41 ± 2.05	12.41 ± 2.35	12.17 ± 1.15	14.96 ± 2.38	15.37 ± 3.17	9.13 ± 0.84	8.99 ± 0.65
CL, L/h	3.94 ± 0.86	4.00 ± 0.44	4.47 ± 0.74	4.41 ± 0.40	5.33 ± 0.63	5.25 ± 1.08	3.91 ± 0.56	4.43 ± 0.55
C_{ss}, μg/ml	–	–	–	–	–	–	17.39 ± 2.68	15.24 ± 1.83
C_{min}, μg/ml	–	–	–	–	–	–	4.22 ± 1.19	3.01 ± 0.88
AUC_{ss}, μg·h/mL	–	–	–	–	–	–	104.32 ± 16.08	91.45 ± 10.97
DF, %	–	–	–	–	–	–	275.50 ± 37.95	295.96 ± 35.02
AI	–	–	–	–	–	–	1.32 ± 0.13*	1.12 ± 0.16*

All values are mean ± SD

T_{max} time to maximum concentration, C_{max} maximum plasma concentration, AUC area under the plasma concentration–time curve, AUC_{0-t} AUC from time zero to the last quantifiabel concentration, $AUC_{0-\infty}$ AUC from time zero to infinity, $t_{½}$ half-life, CL clearance, Vd volume of distribution, C_{ss} steady-state plasma concentration, C_{min} minimum plasma concentration, DF degrees of fluctuation, AI Accumulation Index

* $P < 0.05$

0.13, female: 1.12 ± 0.16, $P < 0.05$); other parameters showed no statistical difference between male and female subjects.

3.3 Tolerability

Single 30-min infusions of 200, 400, and 800 mg of intravenous ibuprofen were well tolerated by all the subjects. In the multiple-dose period, two female subjects reported infusion-site pain during infusion, which happened from the fourth day of multiple doses. The symptoms were rated as mild and considered possibly associated with the study medication. No other adverse events were observed or reported. No clinically significant abnormalities were observed through physical examination, ECG, or laboratory tests.

4 Discussion

Intravenous ibuprofen is a parenteral NSAID approved in the USA in 2009. A growing number of studies demonstrating the favorable efficacy and safety profiles of intravenous ibuprofen for the management of pain and reduction of fever in adult patients are currently available [10, 14–17]. In addition, the pharmacokinetic characteristics of intravenous ibuprofen in a Caucasian population have been reported previously [8, 10, 11]. In this study we investigated the pharmacokinetic properties of intravenous ibuprofen in a Chinese population and we hope this study will add more information to define its pharmacokinetic profile, especially in multiple doses, and the effect of gender on its pharmacokinetics.

It was reported that infusion time greatly influenced the peak concentration of intravenous ibuprofen, which is typically immediately following the end of the infusion [3]. Previously reported studies in Caucasian populations utilized a range of infusion times and dosing levels to evaluate the pharmacokinetic properties of intravenous ibuprofen, which included: a single 60-min infusion of 400 and 800 mg, and a single 30-min infusion of 100, 200, and 400 mg [8, 10]. According to the product labeling, the infusion time of intravenous ibuprofen must be at least 30 min [8]. However, a later pharmacokinetic study indicated that a single dose of 800 mg of intravenous ibuprofen was safe and well tolerated administered over rapid infusion (5–7 min) [11]. The pharmacokinetic parameters were similar with those found after either oral or 60-min intravenous administration, except for the peak concentration, which is much higher than that of a 60-min infusion (120.3 vs. 72.6 $\mu g\ ml^{-1}$) and was achieved much more rapidly [9, 11]. Another more recently conducted study also demonstrated the safety and efficacy of more rapid administration (5–10 min) of intravenous ibuprofen [18, 19]. In the present study, considering the product labeling dosage of intravenous ibuprofen, we selected 30 min as the infusion time and single 200, 400, and 800 mg and multiple 400 mg dosing levels. It was reported that a low ibuprofen clearance was linked to CYP2C9 polymorphisms and subjects homozygous for CYP2C9*3 variant alleles had low ibuprofen clearance rates [20]. A previous study reported the lower frequency of subjects homozygous for the CYP2C9*3 allele in an East Asian population compared with a Caucasian population [21]. The pharmacokinetic profiles of intravenous ibuprofen in a Chinese population observed in the present study accorded with those previously reported in Caucasian populations [3, 9]. However, we failed to include a polymorphism analysis in the present study, which is a limitation of this study.

The present study indicated slight accumulation after multiple doses of 400 mg intravenous ibuprofen every 6 h for 5 days. The AI was 1.22 ± 0.17; C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ after multiple doses increased more than those after single doses significantly. However, it is notable that the plasma ibuprofen concentration was less than 1/20 of the C_{max} 10 h after the last dosing, and undetectable in most of the subjects 12 h after the last dosing. This fact indicated that the slight accumulation had a strong relationship with the dosing interval of 6 h and, furthermore, plasma ibuprofen could be eliminated quickly from the body once dosing ended. Moreover, according to the product labeling, intravenous ibuprofen was clinically recommended to be used continuously for up to 3 days [8]. Therefore, the slight accumulation observed after multiple doses of 400 mg of intravenous ibuprofen in the present study was considered to be of no clinical significance.

The present study compared the pharmacokinetic parameters between male and female subjects and revealed no significant differences between the two groups, with the exception of the AI. More obvious accumulation was observed in male than in female subjects (AI: 1.32 ± 0.13 vs. 1.12 ± 0.16) after multiple doses. However, as we pointed out earlier, the accumulation observed in the present study was considered to be of no clinical significance, and dose adjustments based on sex is not anticipated in clinical use.

5 Conclusions

Similar pharmacokinetic properties of intravenous ibuprofen in healthy Chinese volunteers were observed to those reported in Caucasian populations. Multiple doses of intravenous ibuprofen every 6 h caused slight accumulation. Except for the AI, sex did not affect the pharmacokinetics of intravenous ibuprofen.

Compliance with Ethical Standards

Funding The study was sponsored and funded by Beijing Alica Pharmaceutical Sci-Tech Co. Ltd. (Beijing, People's Republic of China).

Conflict of interest Yali Shen, Feng Nan, Mei Li, Maozhi Liang, Ying Wang, Zhihui Chen, and Zhu Luo declare that they have no financial relationships with any organizations that might have an interest in the submitted work, nor any other relationships or activities that could influence the submitted work.

Ethical approval The study protocol was approved by the Independent Ethics Committee of West China Hospital, Sichuan University (Chengdu, China). Written informed consent was obtained from each subject before screening procedures. All procedures in this study were carried out in accordance with the Helsinki declaration.

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