

A Randomized, Double-Blind, Placebo-Controlled, Single Dose, Crossover Study of the Pharmacokinetics, Safety and Tolerability of Ibuprofen Injection in Healthy Adult Volunteers

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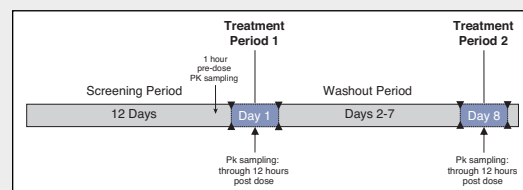
INTRODUCTION

Oral ibuprofen is a widely used, generally well tolerated, and effective NSAID with analgesic, antipyretic and anti-inflammatory properties. However, oral administration is not always practical. An aqueous formulation of ibuprofen, Caldolor® (ibuprofen) Injection, has been approved by the US Food and Drug Administration (FDA) for use in adults for treatment of mild to moderate pain, moderate to severe pain as an adjunct to opioid medications and reduction of fever. Current dosage and administration instructions in the Package Insert indicate that the infusion time must be no less than 30 minutes.¹ However, the medical community has indicated the potential need for information regarding the safety of administering the product over a shorter infusion time, such as 5-7 minutes, along with information on corresponding pharmacokinetic parameters. This study was conducted to evaluate the pharmacokinetics, safety and tolerability of a single dose of intravenous ibuprofen administered over 5-7 minutes compared to a single dose of oral ibuprofen.²

METHODS

This study was a randomized, double-blind, placebo-controlled, single dose crossover study of pharmacokinetics, safety and tolerability of ibuprofen injection in healthy adult volunteers and was conducted in Australia from March 2009 to April 2009 enrolling a total of 12 volunteers. An independent ethics committee approved the study. Participants were screened for eligibility for study participation during the 2 weeks prior to the scheduled dosing date and time.

Figure 1: Study timeline.



Study Design:

Key Inclusion Criteria

- Healthy volunteers between the ages of 18 and 65 years.

Key Exclusion Criteria

- Participants lacking good venous access in both arms.
- History of allergy or hypersensitivity to NSAIDs or any component of intravenous ibuprofen or have never taken aspirin or ibuprofen.
- History of abuse of alcohol or other drugs in the 2 months before study drug administration.
- Have used prescription drugs (not including oral contraceptives) within 14 days before study drug administration or have used aspirin within one week before study drug administration or over-the-counter pain relievers (NSAIDs or acetaminophen) within 3 days before study drug administration.
- Have taken investigational drugs or have donated blood or blood products within 30 days before CTM administration.
- Pregnant or nursing.
- Have had breast cancer.
- Have a clinically significant laboratory test.
- Presence or history of the following conditions: asthma, bleeding

tendency, hypertension, heart failure, peptic ulcer disease, inflammatory bowel disease, or any other gastrointestinal disorder, renal or hepatic disease.

- Have a calculated creatinine clearance (estimated by means of the Cockcroft-Gault equation) of < 75 mL/min.

Study Variables Assessed:

The PK profile of intravenous ibuprofen and oral ibuprofen were evaluated by bioanalysis of plasma samples collected up to 12 hours post-dose in each Period. The PK blood sampling schedule was considered to provide an adequate estimation of the maximum concentration and a reliable estimate of the extent of absorption; that is, the area under the curve derived from direct measurements was anticipated to be at least 80% of the area under the curve extrapolated to infinity for most subjects.

The safety and tolerability endpoints for this study were treatment-emergent adverse events.

Pharmacokinetic Concentration Measurements:

Blood samples for measurement of plasma pharmacokinetic concentrations were scheduled to be collected at the following timepoints in each period (16 samples in each treatment period):

- Period 1: Pre-dose, immediately following completion of intravenous infusion, 15, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose
- Period 2: Pre-dose, immediately following completion of intravenous infusion, 15, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose

Statistical Analysis:

SAS Version 9.1 was used for the preparation of the data listings, the calculation of descriptive statistics for summary tables, and the statistical test procedures.

Plasma pharmacokinetic parameters of ibuprofen were tabulated and plotted for each subject, and summarized with descriptive statistics by dose level. The ratio of the pharmacokinetic parameters C_{max} , AUC_{0-t} , AUC_{0-12} , and $AUC_{0-\infty}$ for oral and intravenous dose forms was determined, and summarized by geometric mean and 90% confidence interval, calculated as the back-transformation of the mean and confidence limits of logarithmic transformed parameters.

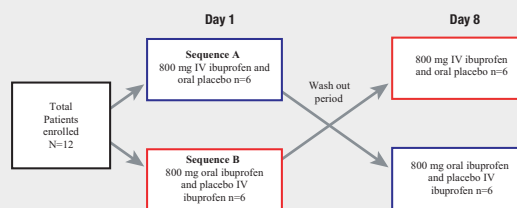
AE data were listed individually and summarized by body system organ class and preferred terms within system organ class (MedDRA). The treatment groups were compared with respect to the numbers of participants reporting AEs, within body systems, unadjusted using Chi-square test and adjusted for center by using the Cochran-Mantel-Haenszel (CMH) test.

Randomization:

In Periods 1 and 2, twelve subjects were randomized in equal proportions to one of two sequences in a randomized, double-blind, placebo-controlled, single dose crossover design:

- Sequence A:** A single dose of intravenous ibuprofen and oral placebo administered concurrently on Day 1 of the Treatment Period followed by a single dose of oral ibuprofen and intravenous placebo given concurrently on Day 8 of the Treatment Period. Days 2-7 were a washout period.
- Sequence B:** A single dose of oral ibuprofen and intravenous placebo administered concurrently on Day 1 of the Treatment Period followed by a single dose of intravenous ibuprofen and oral placebo given concurrently on Day 8 of the Treatment Period. Days 2-7 were a washout period.

Figure 2: Distribution of patients randomized into treatment groups



Dosing

Each subject was scheduled to receive treatment in two periods. Dosing in each period was separated by a minimum 7-day washout. Participants were required to receive the IV infusions in 5-7 minutes and to swallow the oral tablet or capsule within the first minute of the IV infusion.

In each Period, subjects received a single dose of ibuprofen 800 mg, as one of:

- 8 mL intravenous ibuprofen 100 mg/mL added to 192 mL of normal saline, along with placebo capsule;
- 800 mg tablet ibuprofen, along with 200 mL of normal saline IV.

Objectives:

The primary objective of this study was to evaluate the pharmacokinetic (PK) profile of a single dose of intravenous ibuprofen administered over 5-7 minutes. The secondary objective of this study was to evaluate the safety and tolerability of a single dose of intravenous ibuprofen.

RESULTS

A total of 12 patients were enrolled, randomized, and received study medication. All subjects had two cannulas inserted, one in each arm, prior to dosing – one for IV infusion and the other for pharmacokinetic sample collection. All 12 subjects received one dose of ibuprofen 800 mg as intravenous ibuprofen and also one dose of ibuprofen 800 mg as an oral tablet.

Table 1: Summary of Demographics

	Sequence A (Intravenous / Oral)	Sequence B (Oral / Intravenous)	All Subjects
Number of Subjects	6	6	12
Age in years	Average (SD) 35.2 (12.1)	Average (SD) 28.2 (9.0)	Average (SD) 31.7 (10.8)
	Min, Max 18 - 50	Min, Max 21 - 41	Min, Max 18 - 50
Height in cm	Average (SD) 177.2 (5.6)	Average (SD) 178.6 (8.3)	Average (SD) 177.9 (6.8)
	Min, Max 170 - 183.5	Min, Max 165.6 - 186.5	Min, Max 165.6 - 186.5
Weight in kg	Average (SD) 78.0 (10.9)	Average (SD) 75.7 (14.6)	Average (SD) 76.9 (12.3)
	Min, Max 64.8 - 92.6	Min, Max 50.6 - 92.4	Min, Max 50.6 - 92.6
Gender	Female 2	Male 1	Female 3
	Male 4	Female 5	Male 9
Race	Caucasian 6	Caucasian 6	Caucasian 12

Pharmacokinetic Parameters:

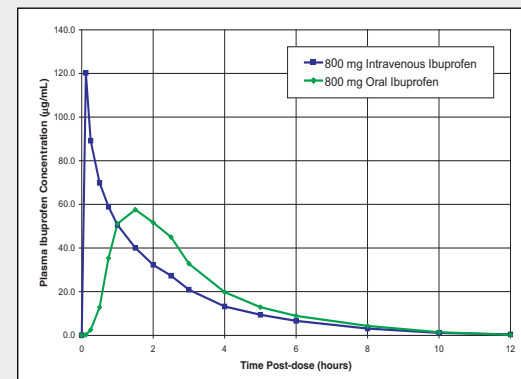
The mean key plasma PK parameters of ibuprofen (IV and oral) are presented by treatment dose form in Table 2.

Table 2: Pharmacokinetic profile of 800 mg Caldolor administration (5-7 minutes) vs. 800 mg oral ibuprofen

Treatment	C_{max} ($\mu\text{g/mL}$)	AUC_{0-12} ($\text{h}\cdot\mu\text{g/mL}$)	AUC_{0-12} ($\text{h}\cdot\mu\text{g/mL}$)	$AUC_{0-\infty}$ ($\text{h}\cdot\mu\text{g/mL}$)	t (h)
Caldolor (ibuprofen) Injection	120 (13)	188 (37)	191 (36)	196 (37)	2.0 (0.5)
Oral ibuprofen	63 (12)	189 (36)	191 (36)	196 (36)	1.9 (0.3)

- The comparison between treatments showed that the oral ibuprofen was 100% bioavailable compared with intravenous ibuprofen, as determined by the mean ratio of geometric least squares means of AUC_{0-12} (90% confidence interval 89.6% - 111.6%).
- The mean C_{max} of intravenous ibuprofen was approximately twice that of the oral dose.
- The median T_{max} of the oral dose was 1.50 hours compared with 0.11 hours (6.5 minutes) for the intravenous infusion over 5-7 minutes.

Figure 3: Pharmacokinetic profile of 800 mg Caldolor administration (5-7 minutes) vs. 800 mg oral ibuprofen



Safety Outcomes:

Table 3: Number of Adverse Events by Intensity and Relationship to Clinical Trial Medication			By Treatment		All Treatments		
			Intravenous ibuprofen 800 mg + Oral Placebo	Oral ibuprofen 800 mg + IV Placebo	Total Number of Treatment-Emergent Adverse Events		
MedDRA System Organ Class (SOC)	MedDRA Preferred Term	MedDRA Lower Level Term	Mild	Mild	Unknown	Not related	Total
General disorders and administration site conditions	Infusion site pain	Infusion site burning	3		3		3
		Infusion site pain	1		1		1
SOC Total			4	0	4	0	4
Injury, poisoning and procedural complications	Post procedural haematoma	Post procedural haematoma		1		1	1
		SOC Total	0	1	0	1	1
Respiratory, thoracic and mediastinal disorders	Epistaxis	Epistaxis		1		1	1
		SOC Total	0	1	0	1	1
Total Number Treatment-Emergent Adverse Events			4	2	4	2	6

Summary of Adverse Events:

- In this study, treatment-emergent adverse events (TEAEs) were reported for 6 of the 12 subjects (50%) during the time from first dose administration to study exit, with a total of 6 adverse events. The number of subjects who reported adverse events was four (33%) for intravenous ibuprofen 800 mg + oral placebo and two (17%) for IV placebo + oral ibuprofen 800 mg. Of the 6 adverse events reported, all were classified as mild.
- A common adverse event, occurring in 3 or more subjects, was infusion site pain which occurred in 4 subjects during infusion when subjects received intravenous ibuprofen.
- All AEs resolved.
- There was no adverse trend in vital signs associated with study treatment.

CONCLUSIONS

- The comparison between treatments showed that intravenous ibuprofen had equivalent bioavailability to oral ibuprofen, as determined by the mean ratio of geometric least squares means of AUC_{0-12} (mean ratio 100%, with 90% confidence interval 90% - 112%).
- The mean C_{max} of Intravenous ibuprofen was approximately twice that of the oral dose.
- The median T_{max} of the oral dose was 1.50 hours compared with 0.11 hours (6.5 minutes) for the intravenous infusion over 5-7 minutes.
- In this study, intravenous ibuprofen was found to be safe and well tolerated when administered over a period of five to seven minutes.

ACKNOWLEDGEMENTS

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