Single-Dose and Multiple-Dose Pharmacokinetics and Dose Proportionality of Intravenous and Intramuscular HPβCD-Diclofenac (Dyloject) Compared with Other Diclofenac Formulations

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Study Objective To evaluate single- and repeated-dose pharmacokinetics (PK) and dose proportionality of hydroxypropyl-β-cyclodextrin (HPβCD)-diclofenac compared with Voltarol after intravenous (IV) and intramuscular (IM) administration.

Design Study 1: Single-dose randomized four-way crossover study. Study 2: Multiple-dose randomized three-way crossover study.

Setting Clinical research center.

Subjects Healthy adult volunteers.

Intervention Study 1: Subjects received HPβCD-diclofenac and Voltarol, IV and IM, with a 5-day washout between treatment periods. Study 2: Subjects received two doses of IV HPβCD-diclofenac and oral Cataflam once every 6 hours for four doses with a 48-hour washout period between treatment periods.

Measurements and Main Results Study 1: IV HPβCD-diclofenac had a higher peak plasma concentration (C_{max}) and earlier time to reach maximum plasma concentration (T_{max}), but equivalent plasma exposure (area under the curve from time zero to t [AUC_{0-t}]) to IV Voltarol. The geometric mean ratio of HPβCD-diclofenac (IV) to Voltarol (IV) for AUC_{0-t} was 106.27%. The geometric mean ratio of HPβCD-diclofenac (IM) to Voltarol (IM) for AUC_{0-t} was 110.91%. The geometric mean ratio of HPβCD-diclofenac (IV) to HPβCD-diclofenac (IM) for AUC_{0-t} was 101.25%. The geometric mean ratio of HPβCD-diclofenac (IM) to Voltarol (IV) for AUC_{0-t} was 104.96%. Study 2: C_{max} for diclofenac was 2904 and 6031 ng/ml after the first IV dose of 18.75 and 37.5 mg HPβCD-diclofenac, respectively, and was 3090 and 5617 ng/ml after the fourth dose, indicating no accumulation. Plasma exposures to 18.75 mg (866 ng·hour/ml) and 37.5 mg (1843 ng·hour/ml) IV HPβCD-diclofenac bracketed that of oral Cataflam 50 mg (1473 ng·hour/ml).

Conclusions Study 1: Bioavailability in terms of AUC after IV administration was equivalent for HPβCD-diclofenac compared with Voltarol and after IM administration of HPβCD-diclofenac and Voltarol. Bioavailability in terms of AUC after IM administration of HPβCD-diclofenac was equivalent to IV administration of HPβCD-diclofenac and IV administration of Voltarol. Study 2: HPβCD-diclofenac showed dose proportionality after single- and multiple-dose administration and no accumulation of HPβCD-diclofenac. HPβCD-diclofenac was safe and well tolerated following IV and IM administration.

KEY WORDS pharmacokinetics, analgesia, diclofenac, Dyloject, Voltarol, hydroxypropyl-β-cyclodextrin, intravenous, intramuscular, oral.
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Balanced inhibition of both cyclooxygenase (COX)-1 and COX-2 by the nonsteroidal antiinflammatory drug (NSAID) diclofenac allows it to be highly effective in decreasing pain and inflammation.[1, 2] Recent studies have further demonstrated that diclofenac opens KCNQ2/3 potassium channels and inhibits sensory neuronal depolarization, resulting in analgesia.[3]

Diclofenac has long been approved as safe and effective for both acute and chronic pain through a variety of routes. However, no injectable diclofenac formulation is currently approved in the United States, in part due to the poor aqueous solubility of diclofenac. Despite its proven efficacy,[4–6] use of the current injectable diclofenac formulation (Voltarol) marketed in Europe, Latin America, and other regions is limited by its cumbersome preparation and administration requirements. These include dilution, buffering with sodium bicarbonate, instability with consequent need for immediate administration following preparation, and slow administration rate (30 minutes to 2 hours).[7] In addition, this formulation uses two organic solvents, propylene glycol and benzyl alcohol, each of which is a known vascular irritant causing pain on injection[8–10] or, occasionally, local necrosis following intramuscular (IM) injection (Nicolau syndrome).[11]

To overcome the poor aqueous solubility of diclofenac, we have used hydroxypropyl-β-cyclodextrin (HPβCD), a solubilizing agent currently used in several other pharmaceutical products.[12, 13] HPβCD-diclofenac (diclofenac sodium solubilized with HPβCD, 37.5 mg/ml) was approved for marketing in October 2007 in the United Kingdom for the treatment or prevention of postoperative pain via intravenous (IV) or IM routes.[14] This ready-to-use HPβCD-diclofenac solution is stable at room temperature and designed to minimize the complexity and risks resulting from multistep preparation and administration of parenteral drugs.[15] Because it lacks irritating organic solvents and may be administered as a single rapid IV bolus injection, the HPβCD-diclofenac formulation optimizes the analgesic efficacy and safety profile of parenteral diclofenac for acute pain.

To evaluate the pharmacokinetics and safety of the HPβCD-diclofenac formulation, we conducted two separate studies in healthy volunteers. Study 1 used different routes of administration in comparison with Voltarol. Study 2 evaluated single and repeated administration of HPβCD-diclofenac in comparison with oral immediate-release diclofenac (Cataflam). The primary objective of these studies was to characterize the pharmacokinetic profile of HPβCD-diclofenac via different routes of administration compared with parenteral and oral formulations of diclofenac during single and repeated dosing. The secondary objective was to assess the safety of HPβCD-diclofenac following IV and IM administration.

Methods

Study Design

Study 1 was a single-dose randomized four-way crossover trial at Simbec Research Limited, United Kingdom. The protocol and informed consent were reviewed and approved by the South East Wales Local Research Ethics Committee, Cardiff Wales, United Kingdom. Study 2 was a multiple-dose randomized three-way crossover study at the Parexel Clinical Pharma-

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All authors performed this work as part of their employment by Javelin Pharmaceuticals Inc. or Hospira Inc. D.B. Carr was the full-time chief medical officer, D.A. Hamilton was the full-time chief operating officer, F. Mermelstein was president, and C. Wright was the EVP of risk management and regulatory affairs for the study sponsor during the time of the study. P.G. Lacouture serves as medical director, pain management, and A. Ramaiya serves as manager, clinical pharmacology, at Hospira Inc.

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cology Research Unit, Baltimore, Maryland. The protocol and informed consent were reviewed and approved by the Chesapeake Research Review, Inc., Columbia, Maryland. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki.

Subjects

Healthy male and female nonsmoker volunteers 18 years of age or older were enrolled, with similar inclusion/exclusion criteria in studies 1 and 2. Females were required to have a negative pregnancy test, be nonlactating, and practice contraception. Subjects were excluded if they had any significant medical history or clinically relevant laboratory test results; were serologically positive for the human immunodeficiency virus, hepatitis B, or hepatitis C; had hypersensitivity to NSAIDs; or were substance abusers.

Study Drugs

HPβCD-diclofenac 75 mg/2 ml (37.5 mg/ml) was administered by IV bolus (approximately 15-second injection into a cannula in the subject's arm) or by deep intragluteal IM injection. Diclofenac sodium 75 mg/3 ml (25 mg/ml) (Voltarol; Novartis Pharmaceuticals UK, Ltd; Surrey, UK) was administered by 30-minute IV infusion and deep intragluteal IM injection. Diclofenac potassium 50-mg tablets (Cataflam; Novartis Pharmaceuticals Corp; East Hanover, NJ, USA) were administered orally.

Subjects were screened 7 to 14 days prior to randomization. Subjects were evaluated prior to each visit to confirm compliance with inclusion and exclusion criteria.

Study Protocol

Study 1

Subjects were randomized to each of four treatments using a computer-generated random sequence: A = one dose of HPβCD-diclofenac 75 mg/2 ml, IV bolus, delivered as previously described; B = one dose of HPβCD-diclofenac 75 mg/2 ml, deep intragluteal IM injection; C = one dose of Voltarol 75 mg/3 ml, 30-minute IV infusion; and D = one dose of Voltarol 75 mg/3 ml, deep intragluteal IM injection. Four treatment sequences were utilized to randomize six subjects per sequence. There was a minimum 5-day washout between treatments.

Study 2

Subjects were randomized to receive each of three treatments in a sequence determined by a computer-generated randomization list: A = HPβCD-diclofenac 18.75 mg IV bolus; B = 37.5 mg IV bolus injection, delivered as previously described; and C = Cataflam 50 mg orally. Each subject received four doses of each of these three diclofenac formulations at 6-hour intervals separated by a 48-hour washout. Study drug administration occurred on days 1, 4, and 7.

Sample Collection

Study 1

Venous blood samples were collected via an indwelling catheter or venipuncture immediately before and at 3, 6, 10, 20, 30, 35, 40, 45, 50, 55, 60, 75, 90, and 105 minutes and 2, 3, 4, 6, and 8 hours after each dose of HPβCD-diclofenac or Voltarol.

Study 2

Venous blood samples were collected immediately before and for 30 hours after the first dose of IV HPβCD-diclofenac or oral Cataflam. Blood samples were obtained via an indwelling IV cannula or venipuncture on days 1, 4, and 7, immediately before and at 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, and 6 hours after the first dose. Later samples were taken immediately before the third and fourth dose and at 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after the fourth dose.

Blood samples from both studies were collected in 5-ml heparinized Vacutainers (BD, Franklin Lakes, NJ, USA) and centrifuged immediately after collection. The plasma was decanted into polypropylene tubes and stored at −20°C until assay.

Assay Methodology for Study 1 and Study 2

Diclofenac plasma concentrations were measured by liquid chromatography with tandem mass spectrometry detection, a method previously validated for the detection of diclofenac in human plasma and urine.[16] The assay used atmospheric pressure ionization with turbo ion spray followed by multiple reaction monitoring of the characteristic deprotonated molecular ion to product-ion transitions for diclofenac and internal standard. This assay was linear from 25 to 30,000 ng/ml. Its

precision ranged from 7.4% to 8.6%, and its accuracy ranged from 100% to 107%.

Pharmacokinetic Analyses for Study 1 and Study 2

Pharmacokinetic parameters were calculated using noncompartmental analysis. Only those plasma concentrations equal to or greater than the lower limit of quantitation (LOQ; 25.0 ng/ml) were used in the analyses. Actual sampling times were used in all pharmacokinetic analyses. Per protocol times were used to calculate mean plasma concentrations for graphical displays.

C_{max} and T_{max} were taken directly from the data. The elimination rate constant, λz, was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The data used for each subject and treatment were determined by visual inspection of a semilogarithmic plot of concentration versus time. Elimination half-life ($t_{½}$) was calculated as

$$t^1/_2 = \frac{0.693}{\lambda z}$$

Area under the curve (AUC_{0-t}) from zero to the final sample with a concentration ≥LOQ (AUC_{0-t}) was calculated using the linear trapezoidal method and extrapolated to infinity using

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_{tf}}{\lambda z}$$

where C_{tf} is the final concentration ≥LOQ.

For each treatment in study 2, the following pharmacokinetic parameters were calculated using noncompartmental analysis:

- First dose: C_{max}, T_{max}, $AUC_{(0-t)}$, and $t_{½}$
- Fourth dose: C_{max}, T_{max}, $AUC_{(0-6)}$, and $t_{½}$

Safety

Safety assessments included adverse event (AE) monitoring, physical examinations, clinical laboratory tests, vital signs, and electrocardiograms (ECGs). Thrombophlebitis assessment by the clinical staff of the subject's IV site at 4 and 8 hours following IV administration was included after IV bolus administration. A 6-point thrombophlebitis grading scale[17] was used (0 = no reaction; 1 = tenderness along the vein; 2 = continuous tenderness or pain with redness; 3 = palpable swelling or thrombosis within the length of the cannula; 4 = palpable swelling or thrombosis beyond the length of the cannula; 5 = as for grade 4, with overt infection).

Statistical Analyses

Study 1

Statistical sample size calculations were conducted using data from previous clinical studies. Within-subject coefficients of variation for natural log-transformed AUC_{0-t} and $AUC_{0-\infty}$ were both approximately 13%, indicating that sample sizes of 16–24 subjects should provide 80% power to obtain 90% confidence intervals within 80% → 125% range if the true difference between observations for the different formulations was 5% or less.

Comparison of AUC_{0-t} and $AUC_{0-\infty}$ between the HPβCD-diclofenac (test) and Voltarol (reference) treatments was conducted on natural logarithms of the primary data using an analysis of variance (ANOVA) model with sequence, subject within sequence, treatment, and period as classification variables.[18] Sequence was tested using subject within sequence as the error term; all other terms were tested using mean squared error. Confidence intervals (90%) were constructed for the ratios (test to reference) of the two parameters using the log-transformed data and the one-sided *t*-test procedures. The point estimates and confidence limits were exponentiated back to the original scale.

Study 2

The analysis used descriptive statistics (mean and standard deviation). Pharmacokinetic parameters were compared for different doses (18.75 and 37.5 mg) and multiple-dose administrations. C_{max} and $AUC_{(inf)}$ for the first dose and C_{max} and $AUC_{(0-6)}$ for the fourth dose were compared across treatments using ANOVA with subject and dose number as classification variables, using the natural logarithm of the data.[18] Pharmacokinetic data from both studies were analyzed using WinNonlin v.3.3 (Pharsight, Mountain View, CA, USA).

Results

Subjects

Study 1

Twenty-four healthy subjects were enrolled. Among them, 22 completed all four phases and

were included in the pharmacokinetic analysis and in the statistical comparisons for which they had data for all treatments.

Study 2

Thirty-six healthy subjects were enrolled. All 36 subjects completed the pharmacokinetic component of the study and were included in the pharmacokinetic analysis.

Pharmacokinetics

Study 1

Consistent with the distinct administration protocols of rapid IV bolus versus 30-minute infusions, mean plasma concentration-time profiles after IV administration differed between HPβCD-diclofenac and Voltarol (Table 1, Figure 1). HPβCD-diclofenac was administered IV over 15 seconds and had a mean C_{max} approximately 4-fold higher (21,524 ng/ml) than the C_{max} for Voltarol (5668 ng/ml) administered IV over 30 minutes. Following IV administration of HPβCD-diclofenac, median C_{max} occurred at 0.05 hours versus 0.5 hours for Voltarol. The mean half-life ($t_{½}$) of diclofenac was equivalent for both formulations, averaging 1.17 ± 0.32 hours for IV HPβCD-diclofenac and 1.23 ± 0.31 hours for IV Voltarol.

Overall exposures to diclofenac for HPβCD-diclofenac and Voltarol were equivalent (mean $AUC_{0-\infty}$ 4420 ± 1636 ng·hour/ml and 4055 ± 694 ng·hour/ml, respectively) with a point estimate and 90% confidence interval (CI) for the geometric mean ratio of HPβCD-diclofenac (IV) to Voltarol (IV) of 105.49% (90% CI 98.88–112.53), demonstrating comparable bioavailability in terms of AUC (Table 2).

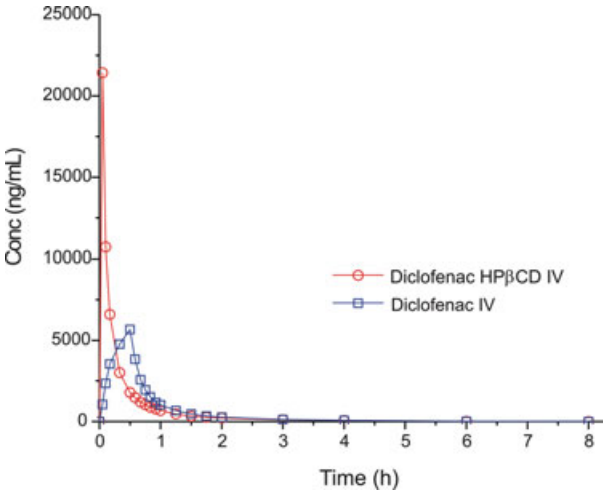

Figure 1. Plasma concentrations of diclofenac following IV administration of diclofenac-HPβCD (HPβCD-diclofenac) and diclofenac (Voltarol).

The mean C_{max} (2569 ng/ml) after IM HPβCD-diclofenac was higher compared with Voltarol IM (C_{max} 1541 ng/ml; Table 1). The higher C_{max} with HPβCD-diclofenac compared with Voltarol after IM administration indicates a more rapid early exposure profile. The median T_{max} following IM administration was 0.642 hours for HPβCD-diclofenac and 0.792 hours for Voltarol. The mean values for HPβCD-diclofenac and Voltarol for $AUC_{0-\infty}$ were 4304 ± 908 ng·hour/ml and 3932 ± 627 ng·hour/ml, respectively, with a point estimate of 107.91% (90% CI 101.05–115.24), demonstrating equivalent bioavailability in terms of AUC after IM administration (Table 2, Figure 2).

The mean C_{max} for Voltarol infused IV over 30 minutes was 5668 ng/ml compared with a C_{max} of 2569 ng/ml for IM HPβCD-diclofenac. The T_{max} for IV Voltarol was 0.5 hours versus 0.642 hours for IM HPβCD-diclofenac. Based on

Table 1. Pharmacokinetic Parameters After Intravenous and Intramuscular Administration of 75 mg HPβCD-Diclofenac and 75 mg Voltarol to Healthy Volunteers

	Intravenous		Intramuscular	
Parameter[a]	HPβCD-Diclofenac Bolus	Voltarol Infusion	HPβCD-Diclofenac	Voltarol
C_{max} (ng/ml)	21,524 ± 30,705 [b]	5668 ± 974	2569 ± 1092	1541 ± 419
T_{max} (hrs)	0.050	0.500	0.642	0.792
AUC_{0-t} (ng·hr/ml)	4363 ± 1600	3970 ± 690	4237 ± 869	3754 ± 609
$AUC_{0-\infty}$ (ng·hr/ml)	4420 ± 1636	4055 ± 694	4304 ± 908	3932 ± 627
$t_{1/2}$ (hrs)	1.17 ± 0.32	1.23 ± 0.31	1.17 ± 0.31	1.71 ± 0.29

C_{max} = maximum observed plasma concentration; T_{max} = time at which C_{max} is observed; $AUC_{(0-t)}$ = AUC up to the last quantifiable concentration; $AUC_{0-\infty}$ = AUC from time zero to infinite time; $t_{½}$ = apparent elimination half-life.

[a]Mean ± SD except for T_{max} for which the median is reported.

[b]Value is higher than expected because one subject had a plasma concentration at the 3-minute blood draw time point that was 10-fold higher than expected. The clinical site deems it possible that the same cannula was used for drug administration and for the 3-minute blood draw for that subject.

this pharmacokinetic data, the IM administration of HPβCD-diclofenac offers comparable delivery.

Overall exposures for HPβCD-diclofenac (IV) and HPβCD-diclofenac (IM) were equivalent ($AUC_{0-\infty}$ 4420 ± 1636 ng·hour/ml and 4304 ± 908 ng·hour/ml, respectively). The point estimate and 90% CI for the geometric mean ratio of HPβCD-diclofenac (IV) to HPβCD-diclofenac (IM) was 100.76% (90% CI 94.24–107.74) (Table 3), indicating equivalent exposure.

Overall exposures for HPβCD-diclofenac (IM) and Voltarol (IV) were equivalent ($AUC_{0-\infty}$ 4304 ± 908 ng·hour/ml and 4055 ± 694 ng·hour/ml, respectively), with a point estimate and 90% CI of 104.69% (90% CI 98.03–111.79) (Table 3).

The mean $t_{1/2}$ following administration of IV HPβCD-diclofenac was 1.17 ± 0.32 hours versus 1.17 ± 0.31 hours after IM HPβCD-diclofenac, suggesting similar disposition profiles with this formulation by both IV and IM routes.

Table 2. Bioavailability of HPβCD-Diclofenac and Voltarol After Intravenous (IV) and Intramuscular (IM) Administration to Healthy Volunteers

Parameter	Geometric Mean Ratio	90% Confidence Interval[a]
HPβCD-diclofenac (IV) vs Voltarol (IV)		
AUC_{0-t}	106.27	99.69 → 113.28
$AUC_{0-\infty}$	105.49	98.88 → 112.53
HPβCD-diclofenac (IM) vs Voltarol (IM)		
AUC_{0-t}	110.91	103.94 → 118.34
$AUC_{0-\infty}$	107.91	101.05 → 115.24

[a]Based on analysis of natural log-transformed data. Geometric mean ratio of HPβCD-diclofenac to Voltarol.

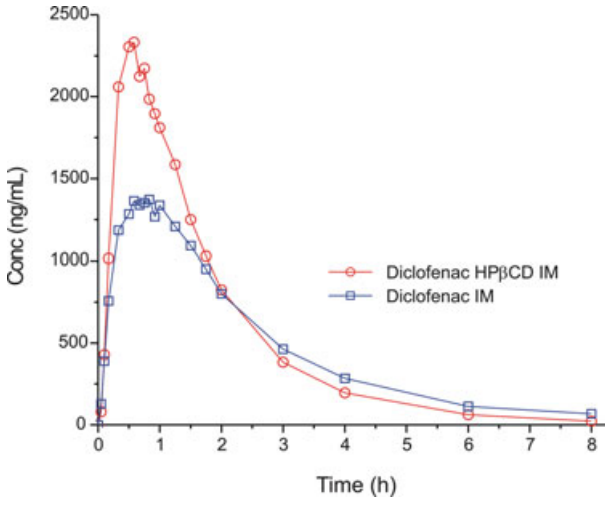

Figure 2. Plasma concentrations of diclofenac following IM administration of diclofenac-HPβCD (HPβCD-diclofenac) and diclofenac (Voltarol).

Table 3. Bioavailability Based on AUC of HPβCD-diclofenac (Intravenous [IV]) versus HPβCD-Diclofenac (Intramuscular [IM]) and HPβCD-Diclofenac (IM) versus Voltarol (IV)

Parameter	Geometric Mean Ratio	90% Confidence Interval[a]
HPβCD-diclofenac (IV) vs HPβCD-diclofenac (IM)		
AUC_{0-t}	101.25	94.86 → 108.06
$AUC_{0-\infty}$	100.76	94.24 → 107.74
HPβCD-diclofenac (IM) vs Voltarol (IV)		
AUC_{0-t}	104.96	98.36 → 112.00
$AUC_{0-\infty}$	104.69	98.03 → 111.79

[a]Based on analysis of natural log-transformed data.

Study 2

Study 2 compared the pharmacokinetics of HPβCD-diclofenac following IV administration of single and multiple doses of 18.75 and 37.5 mg versus oral Cataflam (Figure 3). As expected, mean plasma concentrations were maximal immediately after IV dosing. Oral Cataflam exhibited slower absorption, with a median T_{max} of 1.5 hours (Table 4). The C_{max} following the first IV dose of HPβCD-diclofenac approximately doubled from a mean of 2904–6031 ng/ml for 18.75 versus 37.5 mg. The $AUC_{0-\infty}$ also approximately doubled from a mean of 898–1859 ng·hour/ml across IV doses of 18.75–37.5 mg of HPβCD-diclofenac, demonstrating dose-proportional pharmacokinetics for IV HPβCD-diclofenac. The C_{max} following the

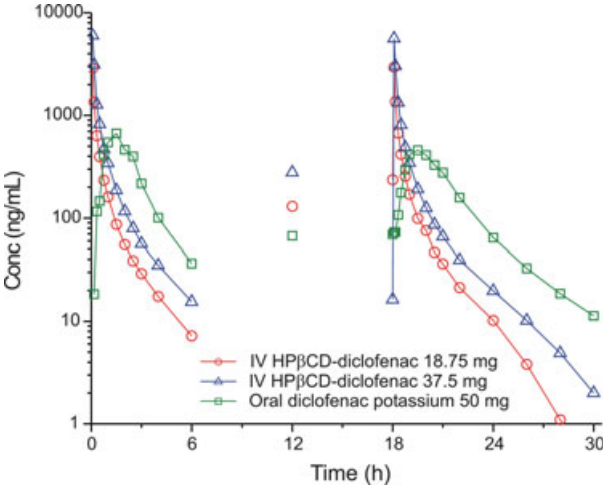

Figure 3. Plasma concentrations of diclofenac following administration of multiple doses of IV diclofenac-HPβCD (HPβCD-diclofenac) and diclofenac potassium (Cataflam) every 6 hours. Concentrations were measured after the first and fourth doses.

Table 4. Summary of Pharmacokinetic Parameters after Single-and Repeated-Dose Administration of Intravenous HPβCD-Diclofenac and Cataflam to 36 Healthy Volunteers

Parameter[a]	HPβCD-Diclofenac (First Dose)		HPβCD-Diclofenac (Fourth Dose)		Cataflam (First Dose)	Cataflam (Fourth Dose)
	18.75 mg	37.5 mg	18.75 mg	37.5 mg	50 mg	50 mg
C_{max} (ng/ml)	2904 ± 661	6031 ± 1178	3090 ± 1029	5617 ± 1799	1246 ± 732	851 ± 462
T_{max} (hrs)	0.083	0.083	0.083	0.083	1.5	1.49
AUC_{0-6} (ng·hr/ml)	866 ± 221	1843 ± 394	935 ± 203	1839 ± 506	1473 ± 488	1350 ± 601
$AUC_{0-\infty}$ (ng·hr/ml)	898 ± 231	1859 ± 376	–	–	1562 ± 519	–
$t_{1/2}$ (hrs)	1.39 ± 0.29	1.44 ± 0.27	1.82 ± 0.48	2.29 ± 0.63	1.28 ± 0.27	2.80 ± 0.66

C_{max} = maximum observed plasma concentration; T_{max} = Time at which C_{max} is observed; $AUC_{(0-t)}$ = area under the curve (AUC) up to the last quantifiable concentration; $AUC_{0-\infty}$ = AUC from time zero to infinite time; $t_{½}$ = apparent elimination half-life.
[a]Mean ± SD except for T_{max} for which the median is reported.

fourth IV dose was 3090 g/ml and 5617 ng/ml, for 18.75 and 37.5 mg, respectively. $AUC_{(0-6)}$ following the fourth dose of 18.75 and 37.5 mg were 935 and 1839 ng·hour/ml, respectively. The C_{max} and AUC following the first and fourth doses were similar, suggesting no accumulation of IV HPβCD-diclofenac. The calculated accumulation factor based on half-life was close to 1, indicating a lack of accumulation during successive doses given every 6 hours, approximately 3.5 × t½.

Plasma exposures to IV HPβCD-diclofenac 18.75 mg (866 ng·hour/ml) and 37.5 mg (1843 ng·hour/ml), as measured by AUC uncorrected for dose, bracketed that after administration of the first oral Cataflam 50 mg dose (1473 ng·hr/ml). This is consistent with the bioavailability of oral Cataflam, which was 64.1% after the first dose and 54.6% after the fourth dose.

The C_{max} after the fourth dose of oral Cataflam 50 mg was 851 ng/ml compared with a C_{max} of 1246 ng/ml following the first dose. The AUC following the first dose was 1473 ng·hour/ml compared with 1350 ng·hour/ml following the fourth dose of Cataflam, suggesting variability in diclofenac's oral absorption. The IV profiles of HPβCD-diclofenac were similar and consistent following the first and fourth dose compared with a substantial decrease in C_{max} from the first to the fourth dose of Cataflam.

Safety

Study 1

No serious AEs occurred during the study. There were no clinically significant changes in clinical laboratory tests, ECGs, or vital signs reported. A total of eight treatment-emergent AEs were reported by five subjects (HPβCD-diclofenac: two subjects; Voltarol: three subjects). The specific AEs for Voltarol included anemia, dizziness, headache, sweating, and vasovagal attack; for HPβCD-diclofenac they included dysgeusia, postural dizziness, and headache. Of the reported adverse events, only one event (dysgeusia following IV administration) was considered "related" to the study drug. All other AEs were considered "not related" or "unlikely to be related" to the study drug and were mild or moderate in severity.

The thrombophlebitis assessment revealed that one subject (1 of 23, 4.3%) given HPβCD-diclofenac had mild irritation (1 = tenderness along the vein) at the 4- and 8-hour time points. Similarly, one subject (1 of 24, 4.2%) had mild irritation (1 = tenderness along the vein) only at the 4-hour time point following Voltarol administration.

Study 2

There were no serious AEs, and none of the subjects were discontinued from the study due to an AE. A total of 14 treatment-emergent AEs were reported by seven subjects; all were mild, resolved spontaneously, and most were unrelated to study treatments. Treatment-related AEs included three mild gastrointestinal events and one instance of mild injection site pain.

None of the chemistry or hematology changes were considered clinically significant. There were no clinically significant changes in vital signs. There were no clinically significant findings or observable differences between treatment sequences for quantitative or qualitative ECG parameters.

Discussion

HPβCD, a cyclic glucose-derived oligomer consisting of linked α-1,4-glucose units, was used to enhance the solubility of diclofenac for

injection.[19] Compared with the previous formulation (Voltarol), this approach allows a reduction in dosing volume and lessened irritation provoked by the nonphysiologic pH and organic solvents.[20] HPβCD has likewise been used to enhance the solubility of poorly soluble drugs such as the marketed antifungal itraconazole[8] and a novel formulation of propofol under development.[9] When diclofenac is solubilized with HPβCD, a therapeutic dose of diclofenac is available in a smaller volume, 75 mg/2 ml versus 75 mg/3 ml as in Voltarol. Furthermore, when Voltarol is to be administered IV, it must first be diluted to 50 to 100 ml.

The effects of route of administration on pharmacokinetics of this novel formulation were examined by comparing IV and IM administration, and by evaluating IV versus a dose-adjusted oral comparison. The first comparison was of the new formulation versus the preexisting product when both were administered IV. We found that AUC_{0-t} and $AUC_{0-\infty}$ were equivalent between HPβCD-diclofenac and Voltarol after IV administration. The 90% CIs for the geometric mean ratios of HPβCD-diclofenac to Voltarol with respect to AUC_{0-t} and $AUC_{0-\infty}$ were well within the accepted 80–125% equivalence window for bioavailability. Thus HPβCD-diclofenac and Voltarol have equivalent bioavailability following IV administration. However, C_{max} was not used in this study to assess equivalence, as the two products differed with respect to rate of administration. Current labeling for Voltarol indicates that the dose be administered over a 30-minute infusion, whereas HPβCD-diclofenac is administered as a rapid IV bolus. As would be expected, C_{max} was higher and T_{max} earlier after HPβCD-diclofenac administration compared with Voltarol. This difference may contribute to the clinical observation of a more rapid onset of analgesia for HPβCD-diclofenac than Voltarol.[21] Despite the higher C_{max}, there was no increased safety risk based on AEs, laboratory tests, and vital signs. These data corroborate a safety meta-analysis of seven single-dose clinical trials[22] that found the incidence of thrombophlebitis observed following IV HPβCD-diclofenac treatment was 1.2% versus 6.5% following IV Voltarol.

When compared for a similar route of administration (IM), AUC_{0-t} and $AUC_{0-\infty}$ were equivalent for HPβCD-diclofenac and Voltarol. The 90% CIs for the geometric mean ratios of HPβCD-diclofenac to Voltarol with respect to AUC_{0-t} and $AUC_{0-\infty}$ were within the 80–125% equivalence window for bioavailability. Thus HPβCD-diclofenac and Voltarol have equivalent bioavailability following IM administration.

Finally, the route and process of administration can be examined for IM HPβCD-diclofenac and IV Voltarol. Of note is that the pharmacokinetics for the different formulations and routes were similar. The longer $t_{1/2}$ following IM administration could be potentially attributed to the flip-flop phenomenon.[23] The flip-flop phenomenon occurs when the process of absorption is the rate-limiting factor in the overall disposition of the drug. The terminal $t_{1/2}$ under flip-flop condition reflects the rate and extent of absorption and is not a true $t_{1/2}$; for Voltarol it can be potentially attributed to the formulation characteristics that result in erratic absorption. The lack of flip-flop phenomenon after IM administration of HPβCD-diclofenac compared with Voltarol could be attributed to superior solubilization using HPβCD versus organic solvents. Due to the extended infusion time for the IV Voltarol, C_{max} was lower compared with IM HPβCD-diclofenac. Furthermore, the AUCs were equivalent.

When developing dosing guidelines, it is important to establish proportionality using the pharmacokinetic profile of a product. Two doses of HPβCD-diclofenac (18.75 and 37.5 mg) within the therapeutic range were examined. The pharmacokinetics were dose proportional after IV administration of both doses, indicating that C_{max} and AUC were dose proportional.

The plasma exposures to 18.75 and 37.5 mg IV HPβCD-diclofenac, as measured by AUC uncorrected for dose, bracketed that after administration of oral Cataflam 50 mg, thus offering the option for transition of therapy from IV for inpatients to oral following their release home from the hospital.

Most products to treat acute postoperative pain require multiple doses, raising concern that repeated dosing many lead to increasing exposure secondary to frequent dosing or a reduced metabolic clearance. However, we found that overall, pharmacokinetic parameters after single and multiple doses did not differ; nor was there evidence for accumulation of diclofenac after IV administration of HPβCD-diclofenac every 6 hours for four doses. Diclofenac is predominantly eliminated via hepatic biotransformation to 4-hydroxy-diclofenac as the major metabolite, a reaction catalyzed by the cytochrome P450 enzyme CYP2C9. The lack of accumulation of diclofenac following IV and IM administration

reduces the potential for clinical drug-drug interactions with substrates and inhibitors of CYP2C9, a genetically polymorphic enzyme.

IV bolus administration of HPβCD-diclofenac did not raise safety concerns. HPβCD-diclofenac administered as 18.75 and 37.5 mg IV boluses every 6 hours over 24 hours was safe and well tolerated.

Recent clinical trials evaluating the use of rapid bolus injections of HPβCD-diclofenac have indicated a faster onset of analgesia compared with other NSAIDs, which is consistent with the pharmacokinetic profile of this new formulation demonstrated in the current study. In two separate double-blind placebo-controlled trials in patients undergoing third-molar extraction, HPβCD-diclofenac had a faster onset of pain relief than either Voltarol[21] or ketorolac.[24] More recently, HPβCD-diclofenac showed a faster onset of action than IV ketorolac in a population of patients having undergone orthopedic surgery.[25]

The lower incidence of thrombophlebitis with HPβCD-diclofenac compared with Voltarol and subsequent reduced need for treatment of adverse events, as well as HPβCD-diclofenac's lack of need for reconstitution, dilution, and buffering prior to each dose compared with Voltarol provide support for potential cost savings with HPβCD-diclofenac compared with Voltarol.[26]

Conclusion

HPβCD-diclofenac, a novel formulation of diclofenac with convenience in both IV and IM dosing, demonstrated a higher peak plasma concentration (C_{max}) and earlier time to peak plasma concentration (T_{max}), as compared with Voltarol. Overall plasma exposures for HPβCD-diclofenac and Voltarol were equivalent. HPβCD-diclofenac was safe and well tolerated, with few AEs reported. Lack of accumulation and linear pharmacokinetics of HPβCD-diclofenac were also demonstrated, which could potentially provide added benefits in patients with complex analgesic regimens or receiving multimodal analgesia.

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