

Pharmacokinetic profile of an intradeltoid diclofenac injection in obese Indian volunteers

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Background: A new propylene glycol-free and reduced-volume formulation of diclofenac sodium 75 mg/mL designed for intradeltoid administration has been found to be bioequivalent to a reference formulation of diclofenac sodium 75 mg/3 mL given via the intragluteal route in normal healthy volunteers. Standard needles may not reach the gluteus maximus muscle in many cases, especially in the obese. The objective of this study was to determine the pharmacokinetic parameters of the new formulation and compare the bioavailability of intradeltoid diclofenac sodium 75 mg/mL with that of the intragluteal 75 mg/3 mL reference formulation in obese volunteers.

Methods: A comparative, two-way, single-dose, bioavailability study was carried out in 10 obese (body mass index > 25) male Indian volunteers after a washout period of seven days. Blood samples were collected until six hours following drug administration and analyzed using a prevalidated high-pressure liquid chromatography method.

Results: The mean maximum plasma concentration and time to reach maximum plasma concentration for the test formulation were 1.30 µg/mL and 0.50 hours, respectively, versus 0.93 µg/mL and 1.08 hours for the reference formulation. The mean areas under the curve from 0 to last measurable time point (AUC_{0-t}) for the test and reference formulations were 2.71 µg·h/mL and 2.73 µg·h/mL, respectively. The mean AUCs from 0 to infinity ($AUC_{0-\infty}$) for the test and reference formulations were 3.71 µg·h/mL and 3.75 µg·h/mL, respectively.

Conclusion: The results suggest that the test formulation of diclofenac sodium 75 mg/mL has an AUC_{0-t} and $AUC_{0-\infty}$ comparable with the reference intragluteal formulation of diclofenac sodium 75 mg/3 mL, but with an earlier time to reach maximum plasma concentration and a trend towards a higher maximum plasma concentration. This could be attributed to faster absorption from the deltoid region than from the gluteal region. The test formulation could be helpful in the management of pain in obese or overweight patients and those with dense subcutaneous fat in the gluteal area.

Keywords: bioavailability, diclofenac, intradeltoid, obese, pharmacokinetics

Introduction

Injectable nonsteroidal anti-inflammatory drugs are commonly used to reduce postoperative pain. They are inexpensive and have been tested over time. They have also been reported to lessen postoperative narcotic requirements and narcotic side effects, including respiratory depression and nausea.^{1,2}

Diclofenac sodium injection is effective and well tolerated in the management of postoperative pain¹⁻³ and is currently marketed worldwide in a 3 mL injectable intramuscular formulation. It is generally administered intragluteally. However, the standard needles used may not reach the gluteus maximus muscle in patients who are obese.⁴⁻⁷

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For optimal effect following intramuscular injection it is important that the drug be delivered to the muscle. Problems can arise if drugs designed to be absorbed from muscle are delivered into subcutaneous tissue. Increasing obesity in developed and many developing countries makes this an important concern.⁷ Other injection sites, such as the deltoid, have been suggested and could be more suitable for these patients. The currently available 3 mL formulation of injectable diclofenac precludes intradeltoid injection due to its larger injection volume.

A new propylene glycol-free and reduced-volume injection of diclofenac sodium has been developed. By using a combination of three classes of solvents containing monohydric and polyhydric alcohols and a polyhydric alcohol ether in combination with water as the principal solvent, it has become possible to dissolve 75 mg of diclofenac in just 1 mL of injection solution without a substantial increase in viscosity. This new formulation, when administered via the deltoid muscle, was observed to have a bioavailability comparable with the intragluteal formulation of diclofenac sodium 75 mg/3 mL in healthy adult Indian subjects.⁸

The bioavailability of this new formulation has not been defined in obese subjects. The World Health Organization has revised the body mass index (BMI) cutoff for Asian Indians, and suggested a BMI of 25 kg/m² to define obesity rather than the 30 kg/m² recommended for Europeans.⁹

The objective of the present study was to determine the pharmacokinetics of the new reduced-volume intradeltoid formulation of diclofenac sodium 75 mg/mL injection and to compare its bioavailability with that of the intragluteal 75 mg/3 mL formulation in adult male Indian subjects with a BMI > 25.

Material and methods

The study was carried out in 10 volunteers with a BMI > 25 at the B.V. Patel Pharmaceutical Education and Research Development Centre, Ahmedabad, India. All subjects provided written informed consent to participate in the study prior to enrolment, and were free to withdraw at any time during the study. The study was approved by the Institutional Ethics Committee and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Subjects

The study population consisted of 10 adult male subjects with a BMI > 25 (mean 26.85, range 25.30–31.16), of mean age 32.3 (25–39) years, mean weight 76.5 (68–89) kg, and mean height 168.7 (163–173) cm.

Design

This study was an open-label, randomized, single-dose, two-way, crossover, comparative bioavailability study that assessed the two injectable formulations of diclofenac under fasting conditions, during two separate dosing periods, with a washout period of seven days between the two periods. The volunteers were administered each of the two study drugs after an overnight fast. Dose administration was performed as per the randomization schedule generated at the B.V. Patel Pharmaceutical Education and Research Development Centre, Ahmedabad, India. Subjects received single doses of the intradeltoid test formulation (diclofenac 75 mg/mL, Troikaa Pharmaceuticals Ltd., India) and the intragluteal reference formulation (Voveran®, diclofenac 75 mg/3 mL, Novartis, India). Intramuscular injections were administered using BD PrecisionGlide needles (Becton Dickinson India Pvt. Ltd., India, 23 G 0.6 × 25 mm) and BD 2 mL Discardit II™ syringes.

Blood sampling

Following administration of the test/reference formulation in each period, a total of 16 blood samples of 6 mL each were collected before dosing and at 10, 20, 30, 40, and 50 minutes, and 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, and 6.0 hours following drug administration. During each session, an indwelling catheter was inserted into a forearm vein. Samples were collected in tubes containing lithium heparinate and immediately centrifuged at 4°C. Plasma was separated and frozen at –70°C until further analysis.

Method of analysis

After the addition of 0.05 mL internal standard (mefenamic acid) 25 µg/mL, 0.5 mL plasma samples were acidified with 0.05 mL 6% trichloroacetic acid. The drug was extracted into dichloromethane 5 mL. The dichloromethane layer was separated and evaporated under nitrogen gas, and then reconstituted in a 0.1 mL mobile phase. A 0.06 mL solution was injected into the column of a high-pressure liquid chromatography system (Jasco 900 series, Japan) equipped with a PU 980 pump, AS 950 autosampler, and UV 975 detector. Separations were achieved using a Grace Vydac 5 µm ODS (4.6 × 250 mm) column (Separations Group Inc, W.R. Grace & Co., Columbia, MD, USA) with a mobile phase consisting of acetonitrile and 0.01 M, pH 6.6 potassium dihydrogen orthophosphate buffer (40:60, % v/v) at a flow rate of 0.8 mL/min under ultraviolet detection at 282 nm. The samples were analyzed at 30°C with a linear range of 0.1–6 µg/mL ($y = 0.3572x + 0.0019$; $r = 0.999$), with an average recovery of 68%. The intraday and between-day

coefficients of variation (%CV) of all the quality control samples were <5% and <4%, respectively. The accuracy of the method was between 90% and 110%. The lowest value on the calibration curve was the lower limit of quantitation, ie, 0.1 µg/mL, and the limit of detection was 0.025 µg/mL.

Pharmacokinetic analysis

The pharmacokinetic parameters measured include the observed maximum plasma concentration (C_{\max}), time to reach C_{\max} (T_{\max}), and the area under the plasma concentration-time curve from 0 hours to the time point of last measurable concentration (AUC_{0-t}) and 0 hours to infinity ($AUC_{0-\infty}$). The C_{\max} and T_{\max} were directly determined from the plasma concentration versus time curves. The AUC_{0-t} from time zero to the last quantifiable point (C_t) was calculated using the trapezoidal rule, and the extrapolated AUC from C_t to infinity ($AUC_{0-\infty}$) was determined as C_t/k_t . $AUC_{0-\infty}$ was calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable concentration to the elimination rate constant (k). Logarithmic transformation was done before data analysis for C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$. Analysis of variance (ANOVA) was used to assess effects. Intrasubject variability in terms of the overall %CV was evaluated from the ANOVA results for Ln-transformed data. For the pharmacokinetic parameters C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$, 90% confidence intervals (CI) for the ratios of test and reference product averages were calculated using ANOVA of the Ln-transformed data. Consistent with the two one-sided tests for bioequivalence, 90% CIs for the ratio of both the product averages were calculated by first calculating the 90% CI for the differences in the averages of the Ln-transformed data and then taking the antilogarithms of the CI obtained.

Safety and tolerability

General clinical safety was assessed via physical examination and vital signs at screening and at the end of the study. Clinical laboratory tests and electrocardiograms were also conducted at screening, before dosing within each treatment period, and at the end of the study. Adverse events were assessed for severity and relationship to treatment throughout the study.

Results

Analytic method

A reverse-phase high-pressure liquid chromatographic method was developed to determine the bioavailability of diclofenac after administration of the two formulations. The calibration range was selected based on expected body concentrations. The method was specific and selective

for the analyte, and good linearity was observed within the range. Sufficient recovery was obtained by extraction under acidic conditions in dichloromethane. The precision and accuracy of the method made it suitable for the intended use.

Pharmacokinetic parameters

The mean plasma concentration-time profiles of diclofenac sodium following administration of single doses to 10 obese volunteers are shown in Figure 1, and a summary of the pharmacokinetic parameters is presented in Table 1. Mean C_{\max} and mean T_{\max} for the test formulation were 1.30 ± 0.18 µg/mL and 0.50 ± 0.16 hours, respectively, and 0.93 ± 0.14 µg/mL and 1.08 ± 0.31 hours for the reference formulation. Peak plasma concentrations reported in the literature have ranged from 1.89 to 2.15 µg/mL following an intramuscular injection of diclofenac 75 mg.^{8,10} Variable values of T_{\max} have been reported, ranging from 3.1 to 6.4 hours for diclofenac sodium with different formulations in healthy subjects.¹¹

The mean AUC_{0-t} for the test and reference formulations was 2.71 ± 0.39 µg·h/mL and 2.73 ± 0.49 µg·h/mL, respectively. The mean $AUC_{0-\infty}$ for the test and reference formulations was 3.71 ± 0.52 µg·h/mL and 3.75 ± 0.58 µg·h/mL, respectively. AUC_{0-t} and $AUC_{0-\infty}$ values are in line with those we have reported earlier for healthy volunteers.⁸

The mean elimination rate constant k_{el} and mean $t_{1/2}$ for the test and reference formulations were 0.11 ± 0.02 h⁻¹ and 6.30 ± 1.27 hours, and 0.12 ± 0.02 h⁻¹ and 5.93 ± 1.11 hours respectively. The point estimate, 90% and 95% CI, and summary of statistics are tabulated in Tables 2 and 3, respectively.

The statistical analysis revealed no significant differences between the test and reference formulations for C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$, suggesting that the pharmacokinetic profile is similar between the two formulations. The %CV corresponding to intrasubject variability was 9.18%, 5.92%, and 7.95% for C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$, respectively. The means (90% CI) of the C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$ for the test:reference ratios were 1.39 (129.8, 151.3), 0.993 (94.6, 104.4), and 0.989 (92.9, 106.08), respectively.

Safety and tolerability

All 10 subjects completed the study, during which there were no premature withdrawals or deaths. No serious adverse events were recorded, and there were no clinically significant changes in vital signs, clinical laboratory variables, electrocardiographic parameters, or physical examination findings during the study.

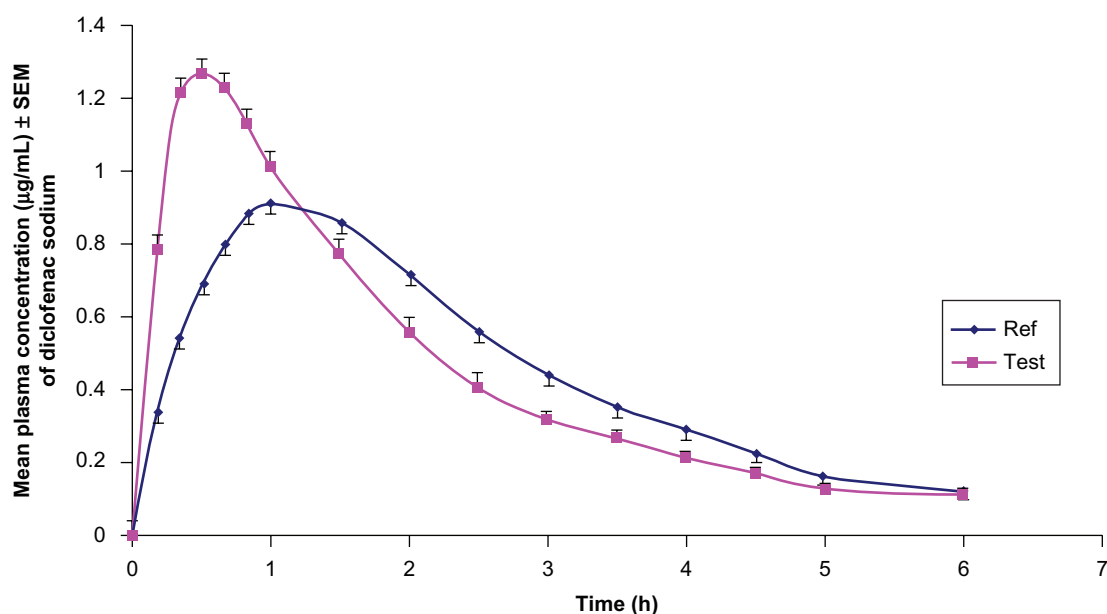


Figure 1 Linear plot of mean plasma concentrations ($\mu\text{g/mL}$) versus time profile of diclofenac sodium for test and reference formulations in 10 obese ($\text{BMI} > 25$) male subjects under fasting conditions.

Abbreviations: SEM, standard error of mean; BMI, body mass index.

Discussion

Depending on the depth of fat, intramuscular injections using standard 35 mm and 25 mm needles may be injected subcutaneously in a significant number of patients, and not into the gluteal musculature. This could alter the pharmacokinetics of the administered medication. Hence, an alternative injection site should probably be chosen to increase the success rate of intramuscular deposition of medication.⁷ The deltoid muscle has been suggested as an alternative site for intramuscular drug administration. Several reports have suggested that this is a better site for injection than the gluteal musculature.^{12,13}

Based on deltoid fat pad thickness determination, it has been observed that for men weighing 59–118 kg, use of a 25 mm needle would result in at least 5 mm of muscle penetration in all subjects. For women weighing less than

60 kg, a 16 mm needle would be sufficient to achieve muscle penetration of 5 mm. For women weighing 60–90 kg, a 25 mm needle would be sufficient, and women weighing more than 90 kg would require a 38 mm needle to enable intramuscular administration.¹⁴ Similar observations were reported by Cook et al,¹⁵ who suggested that in all males and females with a $\text{BMI} < 35$, intramuscular injection into the deltoid could be achieved with a 25 mm needle, whilst in females with a $\text{BMI} > 35$, a 35 mm needle is required. Thus, standard needles would reach the muscle in patients by intradeltoid administration.

To address the need for an intradeltoid route to inject diclofenac sodium, a new formulation containing 75 mg/mL was developed. We have previously reported that the new formulation of injectable intradeltoid diclofenac

Table 1 Mean pharmacokinetic parameters in 10 obese male volunteers following intragluteal administration of the reference formulation (diclofenac sodium 75 mg/3 mL) and test formulation (diclofenac sodium 75 mg/1 mL)

Formulation A (reference)							Formulation B (test)					
	C _{max}	T _{max}	AUC _{0-t}	AUC _{0-∞}	t _{1/2}	k _{el}	C _{max}	T _{max}	AUC _{0-t}	AUC _{0-∞}	t _{1/2}	k _{el}
	(µg/mL)	(h)	(µg·h/mL)	(µg·h/mL)	(h)	(h ⁻¹)	(µg/mL)	(h)	(µg·h/mL)	(µg·h/mL)	(h)	(h ⁻¹)
Mean	0.93	1.08	2.73	3.75	5.93	0.12	1.30	0.50	2.71	3.71	6.30	0.11
SD	0.14	0.31	0.49	0.58	1.11	0.02	0.18	0.16	0.39	0.52	1.27	0.02
%CV	15.53	28.34	17.80	15.53	18.64	17.83	14.18	31.65	14.53	14.02	20.11	20.97

Abbreviations: C_{max} , maximum measured plasma concentration; T_{max} , time of maximum measured plasma concentration; AUC_{0-t} , area under the plasma concentration versus time curve from time zero to the last measurable concentration; $\text{AUC}_{0-\infty}$, area under the plasma concentration versus time curve from zero to infinity; $t_{1/2}$, time required for the plasma drug concentration to decrease by one-half; k_{el} , apparent first order elimination or terminal rate constant; SD, standard deviation; %CV, coefficient of variation.

Table 2 Point estimate, 90% and 95% confidence intervals for the ratio of the product averages of test and reference formulations

Parameter	Point estimate test: Reference	90% confidence interval		95% confidence interval		P value
		Lower confidence limit	Upper confidence limit	Lower confidence limit	Upper confidence limit	
C_{max}	1.39	129.8	151.3	127.4	153.7	0.946
AUC_{0-t}	0.993	94.6	104.4	93.5	105.7	0.135
$AUC_{0-\infty}$	0.989	92.9	106.08	91.5	107.8	0.193

Abbreviations: C_{max} , maximum measured plasma concentration; AUC_{0-t} , area under the plasma concentration versus time curve from time zero to the last measurable concentration; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from zero to infinity

75 mg/mL is bioequivalent to the intragluteal diclofenac sodium 75 mg/3 mL reference formulation.⁸

All 10 subjects completed the study and were included for both statistical and analytic analysis. Based on repeated-measures ANOVA, subject, period, treatment, and interaction term (period \times treatment) showed a nonsignificant difference. The *P* values suggest that there is no statistically significant difference. The 90% CIs for all the pharmacokinetic parameters were within bioequivalence acceptance criteria, with the only exception being C_{max} , for which the upper bound was above the 125% limit.

With regard to the extent of absorption, the AUC_{0-t} and $AUC_{0-\infty}$ were comparable between the test and reference formulations. Mean C_{max} was higher for the test formulation, but this difference was not statistically significant. T_{max} was earlier for the test formulation than for the reference formulation (0.50 hours versus 1.08 hours, respectively). Earlier T_{max} and slightly higher C_{max} may be attributed to the

depth of subcutaneous fat in the gluteal region and better blood flow to the deltoid than to the gluteus muscle.¹⁶

Diclofenac has been reported to be associated with gastrointestinal, cardiovascular, and hepatic side effects.¹⁷ The most common side effects following diclofenac injection are gastrointestinal and pain at site of injection.¹⁸ Mild to moderate adverse events have been reported in about 5% patients with renal colic following intramuscular diclofenac.¹⁹ Only minor gastrointestinal side effects have been reported following intramuscular diclofenac postoperatively.²⁰ In the present study, both formulations were well tolerated, and no adverse events were reported.

Conclusion

Our results suggest that the test formulation of diclofenac sodium 75 mg/mL has a comparable AUC_{0-t} and $AUC_{0-\infty}$ but an earlier T_{max} and a trend towards a higher C_{max} in comparison with the reference diclofenac sodium 75 mg/3 mL formulation. This could be attributed to faster absorption from the deltoid region than from the gluteal region. The test formulation, which can be given by the intradeltoid route using standard needles, would be helpful in the management of postoperative pain and other painful conditions. This formulation would be especially useful in obese or overweight patients and those with dense subcutaneous fat in the gluteal region, in whom intramuscular injections into the gluteus musculature using standard needles may fail to reach the muscle.

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Disclosure

The authors report no conflicts of interest in this work.

Table 3 Summary statistics of diclofenac sodium in 10 obese adult subjects under fasting conditions

Parameters summary statistics	Product	C _{max}	AUC _{0-t}	AUC _{0-∞}
		(µg/mL)	(µg·h/mL)	(µg·h/mL)
Geometric mean	Test	1.29	2.68	3.68
	Reference	0.92	2.69	3.71
LSM	Test	1.29	2.68	3.68
	Reference	0.92	2.69	3.71
LSM ratio B/A %		140.22	99.6	99.19
90% confidence interval: B/A				
Lower limit		129.8	94.6	92.9
Upper limit		151.13	104.4	106.08
P value (ANOVA)				
Period		>0.05	>0.05	>0.05
Formulation		>0.05	>0.05	>0.05
Sequence		>0.05	>0.05	>0.05
Intrasubject variability: %CV		9.18	5.92	7.95

Abbreviations: C_{max} , maximum measured plasma concentration; AUC_{0-t} , area under the plasma concentration versus time curve from time zero to the last measurable concentration; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from zero to infinity; LSM, least squares mean; A, reference product; B, test product; ANOVA, analysis of variance; B/A, bioavailability ratio test (B)/Reference (A); %CV, coefficient of variation.

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