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A Comparative Dermal Microdialysis Study of Diclofenac QPS versus Conventional 1% Diclofenac Gel

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ABSTRACT

The study was designed to evaluate penetration of diclofenac through skin after application of diclofenac 4 % quick penetrating solution (Dynapar QPS) versus conventional diclofenac 1% gel. In this 2 way crossover study, 6 male healthy human subjects were randomized to receive either 1 mg of diclofenac of the Dynapar QPS (25µl) or 1 mg of diclofenac from gel (100 mg) on to the marked area of the forearm three times daily for 3 days. On day 4, after 10th application, the dermal microdialysis was performed. The dialysate samples were collected every half an hour for 6 hours and diclofenac concentration was determined. Mean (± SD) C_{max} after administration of Dynapar QPS was significantly higher as compared to diclofenac gel (11.10 ± 5.18µg/mL versus 2.34 ± 2.84 respectively, P = 0.0058). The time to reach C_{max} was also lesser with Dynapar QPS as compared to diclofenac gel (1.5 ± 0.0 hrs versus 2.17 ± 1.29 respectively, P = 0.2617). The mean AUC_{0-t} and $AUC_{0-\infty}$ after administration of Dynapar QPS was significantly higher as compared to Diclofenac gel (AUC_{0-t}: 9.48 ± 4.76 hr.ng/mL versus 3.53 ± 4.22 respectively, P = 0.0125; $AUC_{0-\infty}$: 10.82 ± 5.03 hr.ng/mL versus 4.74 ± 4.42 respectively, P = 0.0099). There was no statistical significant difference was found in all the secondary pharmacokinetic endpoints such as T_{max}, elimination rate constant and $T_{1/2}$ between both the treatment groups. Dynapar QPS provides higher penetration of diclofenac in underlying tissue as compared to diclofenac gel.

Keywords: Quick penetrating solution, diclofenac 1%, diclofenac 4 %, dermal microdialysis.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the cornerstone for musculoskeletal pain management. [1] Use of NSAID approximately doubles the risk of acute renal failure, and a linear dose-response relationship has been established between use of oral NSAIDs and upper GI bleeding. [2] Around 40% of hospital admissions with upper gastrointestinal bleeding and 40% of associated deaths in older people are related to NSAID use. [3] Topical diclofenac can avoid adverse events associated with oral diclofenac. Topical diclofenac may limit its systemic exposure by acting locally with less systemic distribution. [4] Hence, topical diclofenac is recommended over oral diclofenac by various guidelines. [5-7] Currently available topical formulations of diclofenac include creams, gels or aerosol sprays. Topically applied drugs have to cross the barrier of stratum corneum to reach to the underlying tissue. [8] It is reported that only 10% of diclofenac from the topically applied gel is biologically available and the penetration depth is merely 3-4 mm. [9] Currently available topical formulations have insufficient penetration through stratum corneum, results in failure to provide effective pain relief which mandates the use oral NSAIDs. [10]

Based on the above facts, Troikaa pharmaceutical ltd developed Dynapar QPS using patented QPS (quick penetrating solution) technology. Dynapar QPS is formulated using non aqueous base, non volatile solvents and excipients which increase penetration of the drug across the skin. Increased penetration of diclofenac from Dynapar QPS can provide better efficacy compared to conventional diclofenac gel. We hypothesise that the topical application of Dynapar QPS results in increased penetration of diclofenac in local tissue without compromising safety.

To test our hypothesis, comparative bioavailability study of diclofenac in dermis layer after repeated application of Dynapar QPS versus conventional diclofenac 1% gel using dermal Microdialysis technique in healthy human subjects was conducted. Diclofenac sodium (1% w/w) is one of the most commonly used topical NSAID formulations, in India;

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hence it was selected as a comparator in this study. Dermal microdialysis (DMD) is a unique technique for sampling of topically administered drugs from the site of interest.

MATERIALS AND METHODS

This prospective, randomized, open label, two treatment, two sequence, two period, 2-way crossover comparative bioavailability study was conducted in 6 male healthy human subjects (age 18 to 50 years of age) at the Raptim Research Ltd, Mumbai, India.

All subjects were explained the procedure clearly and were screened for demographic data, medical history, physical examination, 12 lead electrocardiogram (ECG), hematology, biochemistry, serology and urine analysis.

Subject without any sign of abrasion, wound and infection/disease on the skin of hand/at the application site was included in the study. Subjects with normal serological test (human immunodeficiency virus, hepatitis B surface antigen and Hepatitis C virus tests), physical examination, laboratory test (haematological tests, biochemistry, urine analysis) and ECG in correlation with clinical findings were also included. The subject with known hypersensitivity to diclofenac and who has taken systemic or topical analgesics or antihistamines within 72 hours of study Enrollment or systemic or topical corticosteroids within 6 weeks of study Enrollment were excluded.

All subjects provided written informed consent to participate in the study prior to Enrollment, and were free to withdraw at any time during the study.

The study was approved by the Independent Ethics Committee and conducted in accordance with Good Clinical Practice and Declaration of Helsinki. The subjects were enrolled after verification of eligibility criteria. Enrolled subjects were randomized using computer generated balance randomization sheet to receive either 1 mg of diclofenac of the Dynapar QPS (25µl) or 1 mg of diclofenac from gel (100 mg). The randomization schedule was generated at the Raptim Research Ltd, Mumbai, India. 1 mg of diclofenac of the Dynapar QPS (25µl) or 1 mg of diclofenac from gel (100 mg) was applied on to the marked area of the forearm of either left or right hand respectively three times a day for three days with the help of micropipette. After 10^{th} application, the dermal microdialysis was performed using CMA 66 linear probe (on day 4). The procedure for implantation of microdialysis probe was performed by trained physician under sterile condition. Each subject was anesthetized using injection xylocaine 1%, intradermally approximately 10-15 minutes prior to the insertion of microdialysis probe. The probe position was ranging from 1 mm to 4 mm beneath the skin surface (i.e. within the dermis layer). The perfusion rate was kept as 2µL/min throughout the experiment for 6 hours. The total perfusion time was 6 hours. Subjects were remaining in the supine position throughout the study period (6 hours) following the implantation of microdialysis probe on day 4. The dialysate samples were collected every half an hour for 6 hours into CMA 142 Microfraction Collector. At the end of the study, the probes were withdrawn from the skin of each patient and then application site was dressed with povidone iodine solution. The catheter was removed under aseptic conditions. The dialysate sample was analyzed for the concentration of Diclofenac in the Bioanalytical Laboratory at Raptim Research Ltd. The dialysate samples were stored at -80°C and diclofenac concentration in dialysates samples was determined by a pre-validated LC-MS-MS Method. Primary parameters were Cmax, AUC_{0-t} and $AUC_{0-\infty}$ while secondary parameters were T_{max}, $t_{½}$, and K_{el}.

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

Determination of Diclofenac

Dialysate samples were collected and stored at -80°C until analysis. Diclofenac concentration in dialysate samples was determined by a pre-validated with a validated liquid chromatography–Mass Spectroscopy (LC-MS-MS) method developed in the Bio-analytical Laboratory at Raptim Research Limited, Mumbai, India. Diclofenac samples were subjected to analysis using Acetonitrile: 2 mM Ammonium Acetate (90: 10 v/v) as Mobile Phase which was pumped at a flow rate of 0.8 mL/minute using isocratic pump with 70% flow splitting. Volume of Injection was 10µL and autosampler temperature was 10°C. Separation was achieved on a Zorbax XDB C_{18}, 50 × 4.6 mm, 5µl analytical column with retention time of 0.54 minutes for analyte (diclofenac) and run time of 1.20 minutes. API 2000 MSMS was used as a Detector & quantitation was done by 'Peak area method'. All data integration was performed using 'Analyst Software Version 1.4.2'. The slopes, intercepts and correlation coefficients were determined by 'weighted condition (1/x2)'.

Pharmacokinetic analysis

The pharmacokinetic parameters measured include the maximum concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the 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 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 $C_{t/kl}$. $AUC_{0-\infty}$ was calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable concentration to the elimination rate constant (k_{el}).

Pharmacokinetic output from software WinNonlin-Professional version 5.0.1 was used for Analysis. $P<0.05$ will be considered "Statistical significant difference". All the tests will be 2 sided.

RESULTS

The mean dialysate concentration-time profiles of diclofenac sodium following administration Dynapar QPS (test formulation) and Diclofenac gel (references formulation) are shown in Figure 1, and a summary of the primary and secondary pharmacokinetic parameters with p values is presented in Table 1. Mean C_{max} after administration of Dynapar QPS was significantly higher as compared to Diclofenac gel. The mean AUC_{0-t} and $AUC_{0-\infty}$ after administration of Dynapar QPS was significantly higher as compared to Diclofenac gel. The time to reach C_{max} was also lesser with Dynapar QPS as compared to Diclofenac gel, but the difference was not statistically significant. There was no statistical significant difference was found in elimination rate constant and $T_{1/2}$ between both the treatment groups.

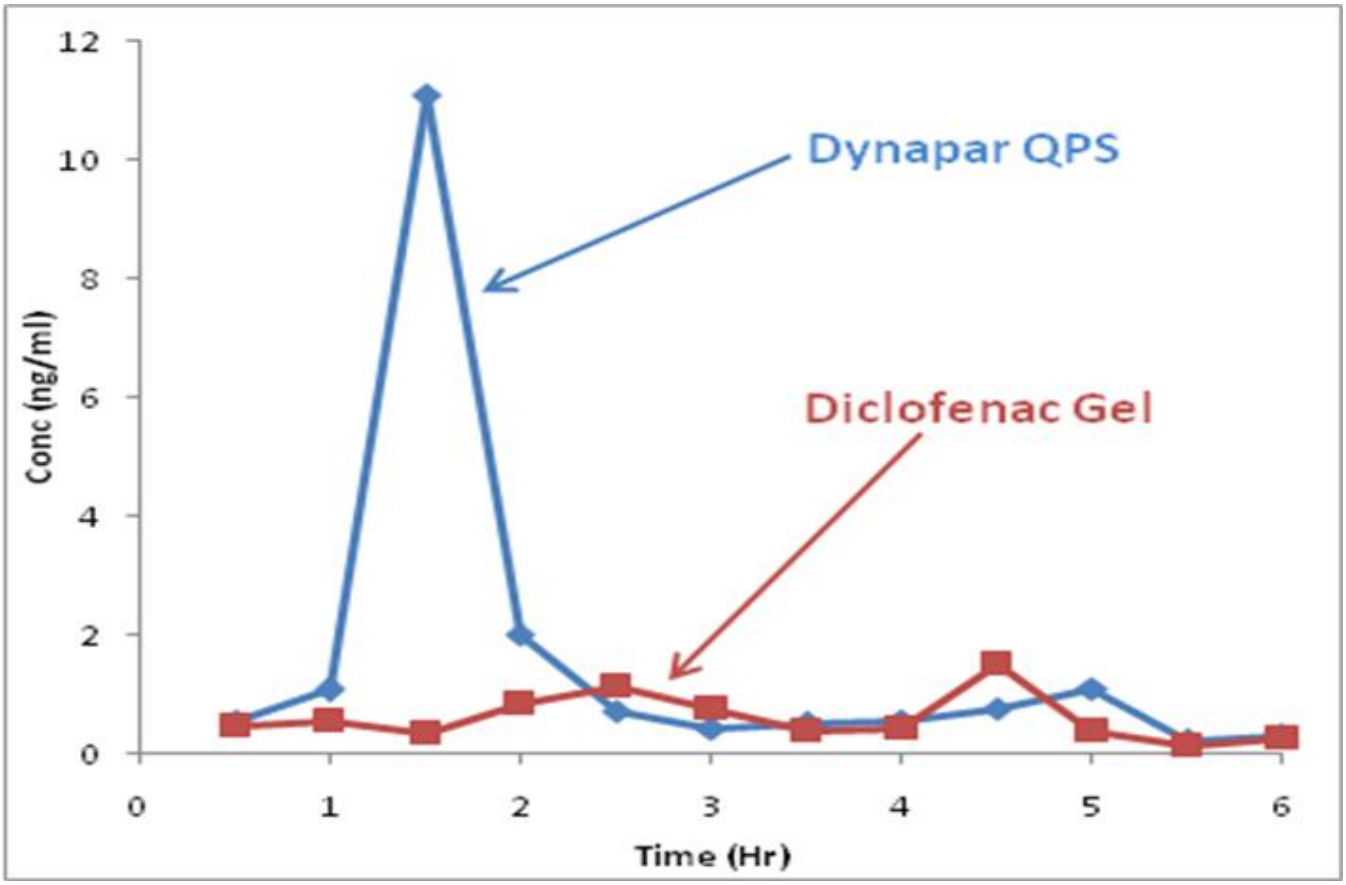

Fig. 1: Mean dialysate concentrations (ng/mL) versus time profile of Dynapar QPS and Diclofenac gel in 6 male healthy subjects

Table 1: Mean pharmacokinetic parameters in 6 male volunteers following topical administration of Dynapar QPS and Diclofenac gel

Pharmacokinetic Parameters (Units)	Dynapar QPS	Diclofenac gel	P value
C_{max} (ng/ml)	11.10 ± 5.18	2.34 ± 2.84	0.0058
AUC_{0-t} (hr*ng/mL)	9.48 ± 4.76	3.53 ± 4.22	0.0125
AUC0-∞ (hr*ng/mL)	10.82 ± 5.03	4.74 ± 4.42	0.0099
T_{max} (hrs)	1.5 ± 0.0	2.17 ± 1.29	0.2617
Elimination rate constant (h^{-1})	0.56 ± 0.12	0.57± 0.50	0.963
$T_{1/2}$ (hrs)	1.30 ± 0.34	1.85 ± 0.96	0.1733

Data were expressed as Mean ± Standard deviation. Data were analyzed by paired "t" test

All subjects were completed the study, during which there were no premature withdrawals or deaths. No case of any local and systemic adverse events was observed and reported during study period. No cases of any abnormality in vital signs, laboratory investigations and physical examination were found during study period.

DISCUSSION

Lack of effectiveness of currently available topical formulations of NSAIDs due to insufficient penetration through stratum corneum compels the use of oral NSAIDs for the management of musculoskeletal pain, despite of their side effects. Dynapar QPS is a novel formulation which increases the penetration of diclofenac through stratum corneum. Our study confirmed that topical application of Dynapar QPS results in increased penetration of diclofenac in local tissue as compared to conventional diclofenac gel without compromising safety.

In our study, the C_{max} after topical application of Dynapar QPS was significantly higher as compared to diclofenac gel. Mean AUC_{0-t} and $AUC_{0-\infty}$ after administration of Dynapar QPS was significantly more as compared to Diclofenac gel. This result indicates higher penetration of diclofenac through stratum corneum after topical application of Dynapar QPS which may enhance the efficacy of diclofenac. It is well established that effectiveness of topical preparation depends on the amount of drug reaching to the site of action. [8]

T_{max} after topical application of Dynapar QPS was lesser as compared to diclofenac gel. Early T_{max} observed after topical application of Dynapar QPS may results in rapid onset of action of Dynapar QPS which is essential in management of acute pain.

In our study, no adverse events were recorded with either study group. Earlier published studies have shown that the topical formulations of diclofenac with higher penetration are safe and do not have significant systemic side effects. [11-12] This can be explained by the fact that increasing penetration of diclofenac in the local tissues does not lead to significant increase in systemic exposure. It has been reported that after repeated administration (three times a day for 7 days) of a topical formulation of diclofenac, the concentration of diclofenac was 3.25 times higher in the subcutaneous adipose tissue and 2 times higher in skeletal muscle tissue compared with oral dosing, whereas relative plasma bioavailability was 50-fold lower. [13] Similar results have also been observed for a topical diclofenac formulated using penetration enhancer. [14]

Our study shows that Dynapar QPS, a novel formulation of topical diclofenac, provides higher penetration of diclofenac through stratum corneum and increased local concentration of diclofenac in underlying tissue as compared to conventional gel formulation of diclofenac without producing any adverse events.

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