DRUG MONITORING
RESEARCH INSTITUTE

BIOEQUIVALENCE OF TRIMETAZIDINE

MAIN REPORT

STUDY TITLE

A randomized two way, two period, two treatment cross over bioequivalence study of TRIMETAZIDINE 35 mg., Tablet TRIVEDON XL manufactured by CIPLA LTD. (INDIA) in comparison with Tablet PREDUCTAL MR 35 mg. manufactured by ANPHARM SA (U.S.A.) in 12 healthy male, adult, human volunteers under fasting condition.

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DATE OF COMMENCEMENT : 20/09/2001
DATE OF COMPLETION : 285/12/2001

SUMMARY

On the basis of the pharmacokinetic parameters C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$ and k_{el} studied, it can be concluded that the Test preparation of TRIMETAZIDINE, Trivedon XL 35 mg., mfg. by CIPLA LTD. (INDIA) is bioequivalent with the Reference preparation, Tablet PREDUCTAL MR, mfg. by ANPHARM SA (U.S.A.). The relative bioavailability of the Test preparation of TRIMETAZIDINE 35 mg. Tablet TRIVEDON XL was 98.95 % of that of the Reference preparation, Tablet PREDUCTAL MR.

INDEX

1. AIMS AND OBJECTIVES :

The aim and the objective of the present study was to evaluate the pharmacokinetic parameters and to compare the bioequivalence of two preparations of Tablet TRIMETAZIDINE 35 mg. in 12 healthy human volunteers in a randomized, two way complete crossover design.

2. SUBJECTS :

Subjects were adult, human, healthy male volunteers the mean age 28.25 ± 3.89 years and mean weight 59.58 ± 8.88 kgs. (Table 1), selected from the panel of volunteers. Volunteers were screened for inclusion in the study within 21 days before the commencement of the study.

They fulfilled the selection criteria as per the protocol submitted earlier. (Annexure I) Before admission to the study each subject was informed of the nature and the risks of the study and a written informed consent was obtained from the volunteers. They were allocated to the treatment A / B (Test or Reference preparation) in accordance with the randomization code.(Table 2)

3 MATERIALS AND METHODS

3.1 STUDY DESIGN :

This was a single dose, randomized, two treatment, two-way cross over study, with a washout period of 7 days between the two dosing sessions. In each dosing session, volunteers received either of the Test or the Reference preparation of TRIMETAZIDINE 35 mg. (3.1) only on the study day at a fixed time.

3.1.1 Dates of the Blood Collection for pharmacokinetic profiles (12 hrs.)

SESSION I	25/09/2001
SESSION II	05/10/2001

3.2 PRODUCT INFORMATION :

Reference Preparation (A) :
Tablet PREDUCTAL MR 35 mg.
containing TRIMETAZIDINE DIHYDROCHLORIDE 35 mg.
Mfg. by ANPHARM SA
Batch No. : IC16602
Exp. Date : 03/2004

Test Preparation (B) :
Tablet TRIVEDON XL
containing TRIMETAZIDINE DIHYDROCHLORIDE 35 mg.
Mfg. by CIPLA LTD.(INDIA)
Batch No. : TZXL3502091
Mfg. Date : 09/2001

3.3 DOSE

With both the preparations the dose was one Tablet containing TRIMETAZIDINE 35 mg. (3.1)

3.4 BLOOD COLLECTION :

All the volunteers assembled in CPU ward at 6.00 a.m. on the study day of each session, after overnight fasting of 10 hrs. Their TPR, BP was recorded and an indwelling intravenous catheter was introduced with strict aseptic precautions in the suitable vein for blood collection. They received either of the study preparations (3.1) according to their code nos. (Table 2).

A total of 15 blood samples were collected at 0 hr. (before drug administration) and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 9.0, 10.0, 12.0, 16.0, 18.0, 24.0 (after drug administration) in the heparinised test tubes at each time point. Breakfast and lunch

was provided after 3 hrs and 6 hrs. respectively after drug ingestion. On the study days volunteers were permitted normal activities, excluding strenuous exercise. Collected blood samples were centrifuged immediately, plasma was separated and stored frozen at - 20°C with appropriate labeling of volunteer code no., study date and collection time.

Abnormal signs / symptoms were monitored, during the study period and for one week after the study period and if noticed, their details were entered in the case report sheets and tabulated at the end of the study.

4. HPLC Analysis

Samples were analyzed by HPLC after extracting the drug from plasma and injecting it on the HPLC column for chromatographic analysis. (HPLC METHOD DETAILS: Annexure 3)

5. PHARMACOKINETIC VARIABLES STUDIED :

Plasma levels of TRIMETAZIDINE for every volunteer at each time point were plotted to obtain Time-Plasma concentration curves for the study preparations. The mean parameters of Bioavailability for this single dose study were :-

C_{max} (Maximum Plasma Concentration)

t_{max} (Time to Maximum Plasma Concentration)

$AUC_{(0-t)}$ (The area under plasma concentration time curve)

$AUC_{(0-inf)}$ (The area under plasma concentration time curve 0 to infinity)

$t_{1/2}$ (Elimination half life)

k_{el} (Elimination constant)

RESULTS, DISCUSSION

AND

CONCLUSION

6. RESULTS :

6.1 Pharmacokinetic parameters for Tablet TRIMETAZIDINE 35 mg.:

Administration of the Reference preparation, Tablet PREDUCTAL MR 35 mg, as a single dose in the fasting state produced the maximum plasma concentration of 129.09 ± 16.25 ng/ ml (C_{max}) at the time 4.17 ± 0.94 hr.(t_{max}) whearas the Test preparation of Tablet TRIVEDON XL, as a single dose in the fasting state produced the maximum plasma concentration 122.40 ± 16.14 ng/ ml (C_{max}) at the time 3.92 ± 1.62 hr.(t_{max}) (Table 5 & 6).

Administration of the Reference preparation, Tablet PREDUCTAL MR 35mg produced the area under plasma concentration time curve (AUC_{0-t}) 1246.52 ± 130.70 ng.hr/ml, whereas administration of the Test preparation of Tablet TRIVEDON XL, produced the area under plasma concentration time curve (AUC_{0-t}) 1233.41 ± 122.89 ng.hr/ml.(Table 7)

When administered as a single dose, in the fasting state, the Reference preparation, Tablet PREDUCTAL MR 35 mg produced the area under plasma concentration time curve upto infinity (AUC_{0-inf}) 1395.80 ± 160.09 ng.hr /ml., whereas administration of the Test preparation of Tablet TRIVEDON XL, produced the area under plasma concentration time curve upto infinity (AUC_{0-inf}) 1395.64 ± 173.19 ng.hr/ml.(Table 8)

Administration of the Reference preparation, Tablet PREDUCTAL MR 35 mg, produced the plasma elimination half life ($t_{1/2}$) 7.33 ± 1.05 hr. whereas administration of the Test preparation of Tablet TRIVEDON XL, produced the plasma elimination half life ($t_{1/2}$) 7.51 ± 1.27 hr. (Table 8).

Administration of the Reference preparation, Tablet PREDUCTAL MR 35 mg, produced the plasma elimination constant (k_{el}) 0.096 ± 0.013 hr^{-1}, whereas administration of the Test preparation of Tablet TRIVEDON XL, produced the plasma elimination constant (k_{el}) 0.095 ± 0.016 hr^{-1}. (Table 8)

On the basis of comparison of the AUC_{0-t} for TRIMETAZIDINE 35 mg., after single dose administration, the relative bioavailability of the Test preparation, Tablet TRIVEDON XL was 98.95 % of that of the Reference preparation, Tablet PREDUCTAL MR 35 mg.

90 % confidence interval (conventional) for C_{max} values of Test preparation of Tablet TRIVEDON XL was 88.53 – 102.61 % of that of the Reference preparation.

90 % confidence interval (conventional) for AUC_{0-t} values of Test preparation of Tablet TRIVEDON XL were 93.71 – 105.37 % of that of the Reference preparation.

90 % confidence interval (conventional) for AUC_{0-inf} values of Test preparation of Tablet TRIVEDON XL were 93.10 – 108.60 % of that of the Reference preparation.

6.2 IN-VITRO DISSOLUTION AND IN-VIVO RATE OF ABSORPTION CORRELATION

In Vitro % dissolution of Test and the Reference preparation of TRIMETAZIDINE tablet were compared with in-vivo rate of absorption. The linear regression analysis was done to compare IN-VITRO DISSOLUTION AND IN-VIVO RATE OF ABSORPTION.

The correlation coefficient for the Reference and the Test preparation was 0.782 and 0.677 respectively. This shows that there is a linear relation between the two preparations.

6.3 STATISTICAL INFERENCE

ANOVA (subject, period, treatment) was applied to the C_{max}, Ln C_{max}, AUC_{0-t}, Ln AUC_{0-t}, AUC_{0-inf} and Ln AUC_{0-inf} values. ANOVA was found to be significant for the subject values of C_{max}, Ln C_{max}, AUC_{0-t}, Ln AUC_{0-t}, AUC_{0-inf} and Ln AUC_{0-inf}.

There was no statistically significant difference for the period and treatment values of C_{max}, Ln C_{max}, AUC_{0-t}, Ln AUC_{0-t}, AUC_{0-inf} and Ln AUC_{0-inf}.

90 % confidence interval (conventional) for C_{max}, Ln C_{max}, AUC_{0-t}, Ln AUC_{0-t}, AUC_{0-inf} and Ln AUC_{0-inf} values of Test preparation of Tablet TRIVEDON XL were within the accepted limit of that of the Reference preparation (i.e. 80 % - 120 %).

Differences and ratios of C_{max}, Ln C_{max}, AUC_{0-t} and Ln AUC_{0-t} were within the normal limits for both the Test and the Reference preparation of TRIMETAZIDINE.

6.4 ADVERSE REACTIONS:

None of the volunteers complained of any adverse reaction on the pharmacokinetic profile days.

7. DISCUSSION :

The single dose bioequivalence study of Tablet TRIMETAZIDINE 35 mg., was conducted in 12 adult healthy, human, male volunteers with two preparations of TRIMETAZIDINE. Values of C_{max}, t_{max}, AUC_{0-t} and AUC_{0-inf} were comparable for the reference and the test preparation in the fasting state.

TRIMETAZIDINE was detected in plasma from 0.5 hour to about 10 hours in the Reference preparation as well as in the Test preparation. Peak plasma levels of TRIMETAZIDINE with the Reference preparation were achieved between 3 to 6 hours whereas with the Test preparation they were achieved between 3 to 8 hours. The mean peak plasma levels of TRIMETAZIDINE with Reference preparation, Tablet PREDUCTAL MR 35 mg on the study day ranged between 100 – 160 ng/ml. while with Test preparation of Tablet TRIVEDON XL ranged between 90 –150 ng/ml. On the basis of comparison of the AUC_{0-t} for TRIMETAZIDINE after single dose administration, the relative bioavailability of the Test preparation of Tablet TRIVEDON XL 35 mg. was 98.95 % of that of the Reference preparation, Tablet PREDUCTAL MR 35 mg.

8. CONCLUSION:

On the basis of the pharmacokinetic parameters studied, it can be concluded that the Test preparation of TRIMETAZIDINE 35 mg. Tablet TRIVEDON XL, mfg. by CIPLA LTD. (INDIA) is bioequivalent with the Reference preparation, Tablet PREDUCTAL MR 35 mg, mfg. by ANPHARM SA (U.S.A.).

PRINCIPAL INVESTIGATOR

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