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ORAL BIOEQUIVALENCE PILOT STUDY OF TRANDOLAPRIL/VERAPAMIL HYDROCHLORIDE EXTENDED RELEASE TABLETS 4/240 mg IN 10 HEALTHY, ADULT, HUMAN, MALE SUBJECTS UNDER FASTING CONDITIONS

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ABSTRACT

The purpose of this study was to compare the pharmacokinetic parameters of Trandolapril/Verapamil hydrochloride Extended Release Film Tablets 4/240 mg of one company with that of the reference product Trandolapril/Verapamil hydrochloride Extended Release Film Tablets 4/240 mg (Tarka®).A validated Liquid Chromatography and Mass Spectroscopy (LC-MS/MS) method was employed for the estimation of Trandolapril and Verapamil in plasma. Pharmacokinetic analysis was done by Non- compartmental method of analysis using the WinNonlin® Version 5.3.The statistical analysis was performed using the SAS® statistical software (version: 9.2). The 90% confidence intervals of the T/R ratio of Ln-transformed $C_{max,\ and}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ were outside the bioequivalence range of 80%-125%. Hence the Test and Reference products of Trandolapril/Verapamil hydrochloride were not bioequivalent. From this study we can conclude that, the combination of Trandolapril/Verapamil hydrochloride (Test) Extended Release Film Tablets 4/240 mg is not bioequivalent to reference Trandolapril/Verapamil hydrochloride (Tarka®).

Keywords: Bioequivalence, Bioavailability, Trandolapril/Verapamil hydrochloride.

INTRODUCTION

Bioavailability is the term used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action [1].Bioavailability is defined as per US Food and Drugs Administration as "the rate at which and the extent to which the active concentration of the drug is available at the desired site of action [2]. Two pharmaceutically equivalent drugs are considered to be bioequivalent when the rate and extent of the active ingredient in the two products are not significantly different under suitable test conditions [3].

When a major formulation change occurs or a generic equivalent of an originator formulation desire market approval, a clinical comparative study is the most obvious to show bioequivalence [4, 5].

Generics are not required to repeat the extensive clinical trials used in thedevelopment of the original, brand-name drug. Instead, generics must show they are bioequivalent to the pioneer (Innovator product) drug and fall into acceptable parameters for bioavailability. There is increased focus on reducing the costs of clinical development, which comprises two-thirds of development costs [6]

Verapamil hydrochloride and trandolapril have been used individually and in combination for the treatment of hypertension. For the four dosing strengths, the antihypertensive effect of the combination is approximately additive to the individual components [7].

Trandolapril and Verapamil is combination of a slow release formulation of a calcium channel blocker

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verapamil hydrochloride and an immediate release formulation of an angiotensin converting enzyme (ACE) inhibitor trandolapril [8-19].

The purpose of this study was to compare the pharmacokinetic parameters of Trandolapril/Verapamil hydrochloride Extended Release Film Tablets 4/240 mg of one company with that of the reference product Trandolapril/Verapamil hydrochloride Extended Release Film Tablets 4/240 mg (Tarka®). In addition, the bioavailability and bioequivalence was evaluated in healthy male human volunteers under fasting conditions.

MATERIALS AND METHODS

Study Design

An open-label, balanced, randomized, two treatment, two sequence, two period, single dose, cross over, oral bioequivalence pilot study under fasting conditions.

Study Type

Prospective Bioequivalence study.

Study centre

Azidus Laboratories Ltd., located at Rathnamangalam, vandalur, Chnnai-48 in collaboration with Institute of Pharmacology, Madras Medical College Chennai.

Sample Size

It is mandatory to do pilot study before doing pivotal study. So I done this study with 10 volunteers.

Study Population

Healthy adult, male subjects.

Study Period

02 period-minimum washout period 5 days

Ethical consideration

The protocol was prepared and submitted to the Independent Ethical Committee, Azidus Laboratories Ltd, Chennai and approval was obtained.

The volunteers were intimated by the word of mouth and were asked to come to Azidus laboratories screening room. They were explained about the study procedure and purpose. Written informed consent was obtained from those who were willing to participate in the study. Then, they underwent screening by medical history, clinical examination and laboratory investigations.

Bio-analytical Methodology

A validated Liquid Chromatography and Mass Spectroscopy (LC-MS/MS) method was employed for the estimation of Trandolapril and Verapamil in plasma. Samples with drug concentration greater than upper limit of the validated range of the analysis were diluted using the appropriate drug free biological fluid and reanalysed by dilution integrity testing.

Statistical Analysis

The descriptive statistics such as mean, standard deviation, geometric mean and coefficient of variation were reported for the relevant pharmacokinetic parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and secondary parameters, T_{max}, $t_{1/2}$ and K_{el} were estimated for both Test and Reference products.

Analysis of variance (ANOVA)

ANOVA was performed using the SAS® statistical software (version: 9.2) General linear model (GLM) procedure. The Ln-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analysed using an ANOVA model with the main effects of treatment, period and sequence as fixed effects. Sum of squares (Type III) was reported and probability values (P) were derived from it. For all analyses, effects were considered statistically significant, if the probability associated with "F" was less than 0.05.

90 % Confidence Intervals (CI)

Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the difference between the test and reference means was calculated for the untransformed data and log transformed data.

Bioequivalence criteria

Based on the statistical results of 90% confidence intervals of the ratios of the means (Test/Reference) for Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, conclusion was drawn to find whether the test product is bioequivalent to the reference product or not.

Bioequivalence was concluded, if the Test to Reference (T/R) ratios and the 90% confidence interval for the ratios for the means fall within the acceptance range of 80% -125% for the pharmacokinetic parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

RESULTS

This single oral dose comparative Bioavailability and Bioequivalence study was undertaken to evaluate the bioequivalence and also, to monitor the adverse events of test product Trandolapril/Verapamil hydrochloride Extended Release Film Tablets 4/240 mg in healthy subjects.

In this two period two way cross over study, 10 subjects who met the study inclusion and exclusion criteria were enrolled but only 09 subjects completed the study entirely.

There was a washout period of 5 days between each of the two periods. The overall duration of the study

was 9 days including the wash out period. Blood samples were collected at the predetermined time points to elicit the pharmacokinetic profiles of Trandolapril/Verapamil hydrochloride.There was no death or serious adverse event reported in this study. One subject reported adverse event (vomiting) with test product.

Pharmacokinetic Parameters

The pharmacokinetic parameters were estimated by using Win Nonlin Software version 5.

Trandolapril:

C_{max}--Peak or maximal plasma concentration (C_{max})

The Test / Reference (T/R) ratio of least square mean of log transformed C_{max} was found to be 123.04% with 90% confidence interval of 99.21% &152.59% therefore 90% CI not in the 80-125% window.

AUC_{0-t}--Area under the concentration-time curve:

The geometric mean ratio ($AUC_T/AUC_{R)}$ was found to be 124.99% and the Confidence Interval for AUC_{0-t} (Test versus Reference) of Trandolapril was found to be 103.02% & 151.65% therefore, 90% CI not in the 80-125% window.

Verapamil

C_{max}--Peak or maximal plasma concentration (C_{max}):

The Test / Reference (T/R) ratio of least square mean of log transformed C_{max} was found to be 62.35% with 90% confidence interval of 44.71% &86.96% therefore 90% CI not in the 80-125% window.

AUC_{0-t}--Area under the concentration-time curve

The geometric mean ratio ($AUC_T/AUC_{R)}$ was found to be 72.22% and the Confidence Interval for AUC_{0-t} (Test versus Reference) of Verapamil was found to be 54.73% & 95.28% therefore 90% CI not in the 80-125% window.

Fig 1. Semilog Plot of Mean PlasmaTrandolapril Concentration Vs Time Points

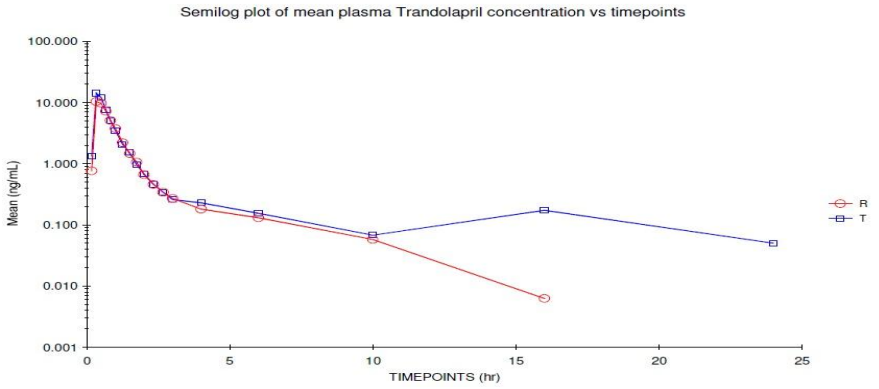

Fig.2 Semilog Plot of Mean Plasma Verapamil Concentration Vs Time Points

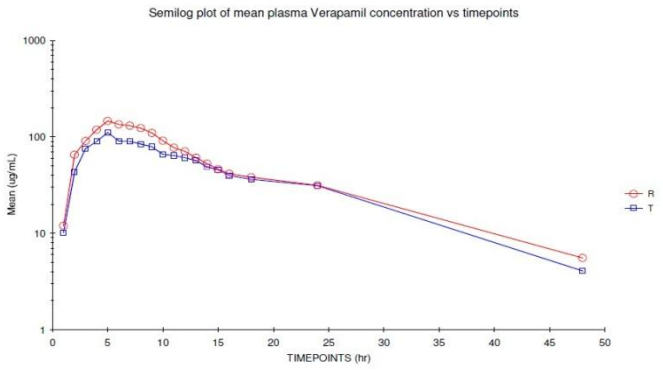

Table 1. Mean values of various pharmacokinetic parameters for Trandolapril

Parameters (Units)	Trandolapril (Mean ± SD)	
	Test	Reference
Cmax (ng/ml)	14.807 ± 6.892	12.973 ± 8.226
AUC0- t (ng.h/ml)	11.542 ± 7.864	8.878 ± 4.115

AUC0-∞ (ng.h/ml)	12.634 ± 8.984	9.153 ± 4.218
Tmax (hr)	0.386 ± 0.085	0.424 ± 0.123
Kel (hr-1)	0.165 ± 0.080	0.443 ± 0.323
T1/2 (hr)	5.317 ± 2.950	2.629 ± 1.971
AUC_%Extrap_obs	7.533 ± 4.416	3.021 ± 1.397

Table 2. Mean values of various pharmacokinetic parameters for Verapamil

Parameters (Units)	Verapamil (Mean ± SD)	
	Test	Reference
Cmax (µg/ml)	117.440 ± 67.569	173.250 ± 80.289
AUC0- t (µg.h/ml)	1618.29 ± 1121.78	1933.99 ± 965.277
AUC0-∞ (µg.h/ml)	2156.81 ± 1133.31	2176.73 ± 1005.32
Tmax (hr)	6.222 ± 2.488	5.666 ± 1.870
Kel (hr-1)	0.062 ± 0.046	0.068 ± 0.027
T1/2 (hr)	19.166 ± 20.507	11.367 ± 3.556
AUC_%Extrap_obs	23.156 ± 25.498	12.419 ± 7.228

DISCUSSION

In this study, Test and Reference product containing Trandolapril/Verapamil hydrochloride Extended Release Film Tablets 4/240 mg were evaluated for the safety upon single dose administration to normal healthy adult male subjects under fasting conditions.

There was a washout period of 5 days between the two periods. The overall duration of the study was 9 days including the wash out period. Blood samples were collected at the predetermined time points to elicit the pharmacokinetic profiles of Trandolapril/Verapamil hydrochloride.

Vital parameters measured at the scheduled time intervals were normal and within the acceptable range of all study subjects..

Trandolapril

The mean C_{max} of Trandolapril, Test (14.807 ± 6.892ng/ml) and Reference (12.973 ± 8.226ng/ml) products showed significant difference.

Similarly, the mean T_{max} of Trandolapril, Test (0.386 ± 0.085 hr) and Reference (0.424 ± 0.123hr) products showed significant difference.

The mean AUC_{0-t} and mean $AUC_{0-\infty}$ of Trandolapril Test and Reference products were also significantly different.

Analysis of variance for Ln-transformed pharmacokinetic parameters revealed that there was significant variation between test and reference formulation for all the three primary pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and$AUC_{0-\infty.}$

The 90% confidence intervals of the T/R ratio of Ln- transformed $C_{max, and}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ were outside the bioequivalence range of 80%-125%.Hence the Test and Reference products of Trandolapril were not bioequivalent.

Verapamil

The mean C_{max} of Verapamil, Test (117.440 ± 67.569µg/ml) and Reference (173.250 ± 80.289µg/ml) products showed significant difference.

Similarly, the mean T_{max} of Verapamil, Test (6.222 ± 2.488 hr) and Reference (5.666 ± 1.870hr) products showed significant difference.

The mean AUC_{0-t} and mean $AUC_{0-\infty}$ of Verapamil Test and Reference products were also significantly different.

Analysis of variance for Ln-transformed pharmacokinetic parameters revealed that there was significant variation between test and reference formulation for all the three primary pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and$AUC_{0-\infty.}$

The 90% confidence intervals of the T/R ratio of Ln- transformed $C_{max, and}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ were outside the bioequivalence range of 80%-125%.Hence the Test and Reference products of Verapamil were not bioequivalent.

The above parameters were outside the range which suggested that Trandolapril/Verapamil hydrochloride Extended Release Film Tablets 4/240 mg Test and Reference were not bioequivalent. So the Test product (generic drug) of Trandolapril/Verapamil hydrochloride Extended Release Tablets 4/240 mg should not reach sufficient bioavailability.

CONCLUSION

- From this study we can conclude that, The combination of Trandolapril/Verapamil hydrochloride (Test) Extended Release Film Tablets 4/240 mg is not bioequivalent to reference Trandolapril/Verapamil hydrochloride (Tarka®).
- Both the test and reference products have comparable safety profile.
- This is only a pilot study, hence it requires more number of subjects to confirm & prove whether the two products are bioequivalent.

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