Bioequivalence and pharmacokinetic comparison between extended release capsules of carvedilol phosphate 40mg: an open label, balanced, randomized-sequence, single-dose, two-period crossover study in healthy male volunteers

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Abstract

An open-labeled, balanced, single-dose, two treatment, two period, two sequence, randomized two way crossover study was conducted in 18 healthy adult male subjects to determine the pharmacokinetic, bioavailability and bioequivalence of carvedilol phosphate 40mg extended release capsules in comparison with Coreg CR™ extended release capsules after single dose administration under fed conditions with a wash-out period of at least 7 days was used. Each volunteer received a 40 mg capsule of the reference (or) test drug respectively. On the day of dosing, blood samples were collected before dosing (at 0.0hr) and 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after dosing. Analysis of carvedilol and its metabolite 4-Hydroxy phenyl carvedilol concentrations was performed using a validated LC-MS/MS method. The pharmacokinetic parameters were analyzed using the non-compartmental model. Drug safety and tolerability were assessed. The primary pharmacokinetic parameters at 90% CI were within the 80 to125% interval required for bioequivalence as stipulated in the current regulations of the USFDA acceptance criteria. The geometric mean ratios (Test/Reference) between the two products of extended-release carvedilol capsule under fed condition were 114.41%(93.68%-116.74%) and 113.15%(96.67%-122.45%) for C_{max} ratios, 101.54%(95.73-104.85%) and 102.72%(95.12% - 113.35%) for AUC_{0-t} ratios and 104.56%(103.24%-107.58%) and 105.73%(95.45%-110.50%) for AUC_{0-inf} ratios of carvedilol and its metabolite 4-Hydroxy phenyl carvedilol respectively. 18 volunteers had completed both treatments. There was no significant difference of the T_{max} parameter between the two formulations (p>0.05). No serious adverse events related to the study drugs were found. This single dose study found that the test formulation carvedilol phosphate ER capsules is bioequivalent in terms of rate and extent of absorption to the reference formulation Coreg CR™ ER capsules of 40 mg under fed condition in healthy adult male volunteers according to the USFDA regulatory guidance.

Materials and Methods

Study drugs:

Carvedilol phosphate ER Capsules and Coreg-CR™ Extended-release Capsules from GlaxoSmithKline were used as the test and the reference products respectively. Both products were prepared as Carvedilol phosphate equivalent to Carvedilol 40 mg. Both the products were stored at controlled room temperature 25˚C (77 ˚F).

Study population:

The study was carried out at Actimus Biosciences Private Limited, India. The study protocol was approved by the Ethics Committee. In addition, the protocol was performed in accordance with the Declaration of Helsinki Principles as outlined in the ICH-E6 Guidelines for Good Clinical Practice (GCP). All subjects were given a detailed description of the study and written informed consent was obtained prior to the enrollment. The sample size was estimated based on, Coefficient of variation (C.V.) of the drug, sufficient statistical power to detect 20% difference with the power of 0.8 in C_{max} and AUC between the test and reference product, Regulatory requirements. Sample size was based on estimates obtained from reported literature and previous studies. Assuming a formulation ratio (T/R) ranging from 0.95-1.05 a sample of 18 subjects including dropouts would be sufficient to show bioequivalence between the two formulations with a power of at least 80%. Hence sample size of 18 subjects was enrolled in the study. 18 healthy male volunteers between the ages of 18-45 years with a body mass index between 18.5 kg/m^2 and 24.9 kg/m^2, with body weight equal to or not less than 50 kg were assessed to be in good physical condition by a complete medical screening including a medical history, physical examination, chest radiography, electro radiography, laboratory screening test for hematologic and blood biochemistry parameters and nonsmoker status. Subjects with a history of hypersensitivity to any ingredients in the carvedilol products and/or related drugs or its constituents or who were taking any medication or alcohol for a 21-day period prior to the study were excluded. Subjects who had a history of cardiovascular, hepatic, renal, gastrointestinal or hematologic disease were excluded from the study.

Study design:

The study was an open-labeled, single-dose, study taken with food, two-treatment, two-period, two-sequence randomized two way crossover with at least one week washout period. Subjects were randomly allocated to two groups by the sequence of product administered [Test-Reference (TR) and Reference-Test (RT) group]. In each period, 1X40mg ER capsule of carvedilol phosphate of the test or reference product was administered 30 minutes after starting a high fat, high calorie breakfast at the same time in the morning before dosing. Subjects were housed 12 hours prior to dosing in the clinical facility from a time adequate to ensure 10 hours supervised fasting before consuming high fat breakfast and were allowed to leave the facility after 24.00 hours post-dose sample in each period. The subjects received a standard meal at about 4.0, 9.0 and 13.0 hours after dosing in each period. During housing, all meal plans were identical for all the periods.

Drinking water was not allowed from one hour before dosing till one hour post-dose (except for 240 ± 02 mL of drinking water given for dosing). Before and after that, drinking water was allowed at ad libitum. After a minimum of 1 week washout period, the subjects were crossed over to the next treatment following the same procedure as conducted in the 1st period.

Sample collection:

During dosing day in each period, 23 blood samples (6 mL each) will be collected as per the following schedule: Pre dose sample(0.00 hr) within 02 hrs prior to drug administration and the others at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post dose. The total volume collected per study participant in this study will not exceed approximately 321 mL including up to 9 mL for screening, and 7-9 mL for post clinical assessment of lab parameters and 18 mL for discarded blood sample resulting from use of intravenous cannula for 12 hours and 2-9 mL was collected for repeat/additional lab tests, if required. For separating plasma, all blood samples were centrifuged at 3800 RPM for 10 minutes at 4°C ± 2°C. Centrifugation of all samples was done as early as possible after each sample draw time point. After centrifugation, plasma samples were aliquoted into two sets in properly labeled polypropylene tubes and immediately stored at about -60°C or colder.

Results

Study population:

18 healthy male adults eligible for the study enrollment were randomly divided into 2 groups [Test-Reference (TR) and Reference-Test (RT)] according to the sequence of drug administration. All the subjects had completed both the periods. Thus, this study was balanced in each sequence and the results from 18 volunteers were used for pharmacokinetic and statistical analysis. Table-1 demonstrates the demographic characteristics of the volunteers.

Bio analysis and pharmacokinetics:

The LC/MS/MS system consisted of four pumps for gradient solvent delivery, and a divert valve to direct LC effluent to the mass spectrometer in the analyte elution window. The analytical column effluent is directed through the divert valve to a thermo electron TSQ quantum discovery mass spectrometer. The instrument was operated in the positive ion mode. The precursor [M·H]+ ions at m/z 407.113, 423.528 and 260.200 for Carvedilol, 4-Hydroxyphenyl Carvedilol and Propranolol respectively were selected by the first quadrupole (Q1). After collision-induced fragmentation in Q2, the product ions at m/z 224.503, 100.344 and 116.100 for Carvedilol, 4-Hydroxyphenyl Carvedilol and Propranolol, respectively, were monitored in Q3.A resolution of one unit (at half peak height) was used for both Q1 and Q3. The method was fully validated using these Q1 and Q3 masses for both compounds with satisfactory results. Linear calibration curves were obtained with a coefficient of correlation (r2) usually higher than 0.995 in range of 0.1 ng/mL to 250 ng/mL. For each calibration standard level, the concentration was back calculated from the linear regression curve equation. No significant difference was observed in any of the analyzed pharmacokinetic parameters for Carvedilol and its metabolite 4-Hydroxyphenyl Carvedilol was shown in Table 2.

Bioequivalence analysis:

Ninety percent confidence interval of geometric mean ratios of bioavailability parameters between the test and reference formulation are presented in Table 3. The statistical analysis obtained from this study showed that the point estimate (90% CI) of the geometric mean ratio (GMR) (T/R) of C_{max}, AUC_{0-t} and AUC_{0-inf} was entirely within the equivalence criteria (80.00-125.00%) which was 114.41% (93.68%-116.74%) and 113.15% (96.67%-122.45%) for C_{max} ratios, 101.54% (95.73-104.85%) and 102.72% (95.12%-113.35%) for AUC_{0-t} ratios and 104.56% (103.24%-107.58%) and 105.73% (95.45%-110.50%) for AUC_{0-inf} ratios of carvedilol and its metabolite 4-Hydroxyphenyl Carvedilol respectively. In addition, no significant difference of the T_{max} parameter between the two studied formulations was observed (p >0.05). Therefore, it was concluded that the two extended-release capsule formulations of carvedilol were bioequivalent in terms of rate and extent of absorption for the drug carvedilol and the metabolite data has been given as supportive evidence. The mean plasma concentration vs time profiles were given in Fig 1.

Tolerability:

Almost all volunteers taking both carvedilol formulations were noted for mild adverse events. Most common events were drowsiness, nausea and loss of appetite. However, no subject had any severe adverse event or withdrew from the study because of an adverse event.

Category		Treatment: Test (T)	Treatment: Reference (R)	Total
Age (years)	Mean ± SD	22.44 ± 4.37	22.44 ± 4.37	22.44 ± 4.37
	Range	18.0 – 35.0	18.0 – 35.0	18.0 – 35.0
	Median	23	23	23
	N	20	20	20
Age Groups	< 18	0	0	0
	18 – 40	20	20	20
	41 – 64	0	0	0
	65 – 75	0	0	0
	> 75	0	0	0
Gender	Female	0	0	0
	Male	20	20	20
Race	American	0	0	0
	Hispanic	0	0	0
	Caucasian	0	0	0
	Asian	20	20	20
Height (cm)	Mean ± SD	165.48 ± 4.89	163.12 ± 5.69	164.3 ± 5.57
	Range	159.0 – 176.0	155.0 – 175.0	155.0 – 176.0
	Median	168	162	165
	N	20	20	20
Weight (kg)	Mean ± SD	65.46 ± 6.43	59.76 ± 6.24	62.61 ± 6.41
	Range	52.0 – 77.0	52.0 – 70.0	52.0 – 77.0
	Median	59	58	59
	N	20	20	20
BMI (kg/m^2)	Mean ± SD	21.10 ± 1.79	22.86 ± 1.46	21.98 ± 1.62
	Range	20.0 – 24.9	20.1 – 24.8	20.0 – 24.9
	Median	21.6	22	21.8
	N	20	20	20

Table No 1: Demographic characteristics

Pk Parameters	Carvedilol: Test	Carvedilol: Reference	4-Hydroxy phenyl Carvedilol: Test	4-Hydroxy phenyl Carvedilol: Reference
Cmax (ng/mL)	32.421	37.821	5.845	6.494
AUCt (ng.h/mL)	239.95	248.616	39.872	43.44
AUCinf (ng.h/mL)	272.713	266.912	47.440	66.141
Tmax (hr)	5.173	5.049	5.136	5.073
kel (1/h)	0.125	0.143	0.097	0.093
t1/2 (hr)	5.857	5.348	7.326	9.146

Table No 2: Pharmacokinetic Parameters of Carvedilol & 4-Hydroxyphenyl Carvedilol for Both Formulations

Parameter	Carvedilol: C_{max}	Carvedilol: AUC_t	Carvedilol: AUC_{inf}	4-Hydroxyphenyl Carvedilol: C_{max}	4-Hydroxyphenyl Carvedilol: AUC_t	4-Hydroxyphenyl Carvedilol: AUC_{inf}
90% CI Lower Limit	93.68	95.73	103.24	96.67	95.12	95.45
90% CI Upper Limit	116.74	104.85	107.58	122.45	113.35	110.50
T/R Ratio (%)	114.41	101.54	104.56	113.15	102.72	105.73
Power	0.91	1.00	1.00	0.95	0.98	0.98
Intra Subject Variability	11.34	5.10	5.07	6.62	5.08	6.82
Inter Subject Variability	28.48	52.04	51.49	29.58	30.01	28.91
ANOVA (p-Value)						
Sequence	0.1922	0.1771	0.1866	0.6120	0.1966	0.1277
Period	0.2018	0.2241	0.5355	0.0031	0.3054	0.1335
Treatment	0.9424	0.4115	0.2960	0.5610	0.9205	0.5353

Table No 3: Bioequivalence Parameters for Carvedilol & 4-Hydroxyphenyl Carvedilol

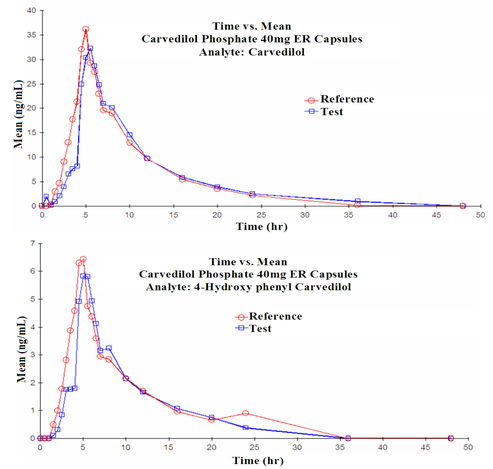

Fig. 1: Mean Plasma Concentration Vs Time profile for Carvedilol & 4-Hydroxyphenyl Carvedilol

Conclusion

This single dose study found that the test formulation carvedilol phosphate 40mg Extended Release Capsules is bioequivalent to the reference formulation Coreg CR™ Extended Release Capsules the extent and the rate of absorption, of 40mg under fed condition in healthy adult male volunteers according to the USFDA regulatory guidance.

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