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Research Study *Open Access*

A Study on Pharmacokinetic Drug - Drug Interactions between Albuterol with Beta Blocker Carvedilol in Wistar Rats

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ABSTRACT

Patients with cardiovascular diseases are often treated by concurrent multiple drug therapy. It is therefore plausible that with an increasing number of drugs the risk of drug interactions increases. Such interactions can be either pharmacodynamic (and are due to the mechanism of the administered drugs) or they can be pharmacokinetic (resulting in a reduction or enhancement of drug elimination). Pharmacokinetic interactions can be either due to interactions at the level of drug metabolizing enzymes (most important cytochrome P450 (CYP) enzymes) or interactions at the level of drug transporter proteins (for example P-glycoprotein (MDR1)). It is important to distinguish between both mechanisms because interactions at transporter proteins can be attributed to those drugs that are not enzymatically metabolized. The present study was aimed to conduct to evaluate any possible pharmacokinetic interactions between albuterol and carvedilol in male wistar rats. The results were showed no significant difference in the t_{max} of Carvedilol alone and combination with albuterol on day 1 and day 8 respectively. These were no significant difference in both c_{max} and t_{max} of albuterol alone and combination of Carvedilol on day 1 and day 8 respectively. And there was no significance difference in AUC_{0-t} and AUC_{o-inf} also in alone and combination of both drugs on day 1 and day 8th. Based on the results obtained from kinetic study it is evident that the single dose of albuterol and Carvedilol individually and concomitantly treated shows no statistically significant interactions in its pharmacokinetic parameters.

Keywords: Albuterol, carvedilol, Pharmacokinetic parameters, Drug-drug interactions (DDIs)

INTRODUCTION

Drug-drug interactions (DDIs) are one of the commonest causes of ADRs and we reported that these manifestations are commons in the elderly due to poly-therapy [1, 2, 3, 4]. In fact, poly-therapy increases the complexity of therapeutic management and thereby the risk of clinically relevant drug interactions, which can induce the development of ADRs, and both reduce [5, 6] or increase the clinical efficacy [7, 8].

Poly-therapy may determine the "prescribing cascade," which occurs when an ADR is misunderstood and new potentially unnecessary drugs are administered; therefore the patient is at risk to develop further ADRs [9].

Albuterol sulfate is a synthetic, sympathomimetic β2-agonist that causes relaxation of bronchial, uterine, and vascular smooth muscles. It is one of several adrenergic compounds developed for the treatment of asthma in humans [10]. Albuterol is 40 available in both oral and aerosol forms, although intravenous, intramuscular, and subcutaneous methods of administration have been reported in the literature.

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of Carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability.

The present study was aimed to conduct to evaluate any possible pharmacokinetic interactions between albuterol and Carvedilol.

MATERIALS AND METHODS

Materials

Drugs and chemicals

Albuterol, Carvedilol, were procured from aurobindo laboratories as a gift sample. All HPLC grade solvents (methanol and water) were procured from finar chemicals Ltd., Ahmedabad. All chemicals used were analytical grade.

Animal study

Male Wistar rats (weighing 200-220gms) were procured from the animal house CMR College of Pharmacy, Hyderabad. Animals were randomly divided into three groups each group contains six animals. Each rat was maintained under controlled lab environment atmosphere humidity of 50%, fed with standard pellet diet and water *ad libitum*. The protocol of animal study was approved by the institutional animal ethical committee with IAEC no: IAEC/1657/CMRCP/T2/Ph D-16/75.

Study Design

The rats were grouped as follows

Group I : Albuterol alone in single dose / day in healthy rats.

Group II : Carvedilol alone in single dose / day in healthy rats.

Group III : Albuterol and Carvedilol concomitant administration as a single dose / day in healthy rats.

Collection of Blood Samples

After administration of the drugs, blood samples of 0.5ml were drawn from each anesthetized (isoflurane) rat at pre-determined time intervals was collected from the retro-orbital plexus using a capillary tube into pre-labelled eppendorf tubes containing 10% of K_2EDTA anticoagulant (20µL). The time intervals for the sample collection were 0 (Pre dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 18 and 24 hrs (post dose), Equal amount of saline was administered to replace blood volume at every blood withdrawal time.

Plasma was obtained by centrifuging blood samples by using cooling centrifuge (REMI ULTRA) at 3000rpm for 5 minutes. The obtained plasma samples were transferred into pre-labelled micro centrifuge tubes and stored at −30°C until bio analysis of pharmacokinetic and pharmacodynamic parameters. As described above, all the procedures were followed on day 8 also. Pharmacokinetic parameters were calculated by non-compartmental analysis by using Win Nonlin® 5.1 software. Concentrations obtained from the above bio-analytical method were compiled.

Method of Analysis

Preparation of Plasma Samples for HPLC Analysis

Rat plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5ml

of ice-cold absolute ethanol for each 0.5ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1min. After centrifugation (5000 – 6000rpm for 10min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200µ1 of mobile phase was injected for HPLC analysis.

For HPLC an Inertsil ODS 3V, 250x4.6 mm, C18 (250 mm x 4.6 mm, 5µm) column with 5µm particle size and the mobile phase consisting of a mixture of The mobile phase consisted of Methanol: Acetonitrile: 1% OPA in the ratio of 80:18:2 v/v/v a flow rate of 1 ml/min. and . The UV detection wavelength was 240nm and 20µl sample was injected. Hydrochlorothiazide used as internal standard. The retention times of Carvedilol, Albuterol & Hydrochlorothiazide were found to be 2.1, 4 and 6 min respectively.

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The $AUC_{0-\alpha}$ was calculated using the formula $AUC_{0-t} + [C_{last}/K]$ where C_{last} is the concentration in µg/ml at the last time point and K is the elimination rate constant.

Various pharmacokinetic parameters like area under the curve [AUC], elimination half-life [t½]. Volume of distribution (V/f) total clearance (Cl/f) and mean residence time for each subject using a non-compartmental analysis by using Win Nonlin® 5.1 software.

STATISTICAL ANALYSIS

Statistical comparisons for the pharmacokinetic – Pharmacodynamic study among, Albuterol, Carvedilol alone and in combination groups and plasma concentration – response study among concentrations and time were carried out with student's paired T-Test a value of $P<0.05$ was considered to be statistically significant. Data were reported as mean ± S.E.M linear regressions were used to determine the relationship between total plasma concentrations and pharmacokinetic and pharmacodynamic parameters. The mean concentration versus time profile of Albuterol, Carvedilol in rat plasma is shown in **Figures 1, 2, 3, and 4.**

RESULTS AND DISCUSSION

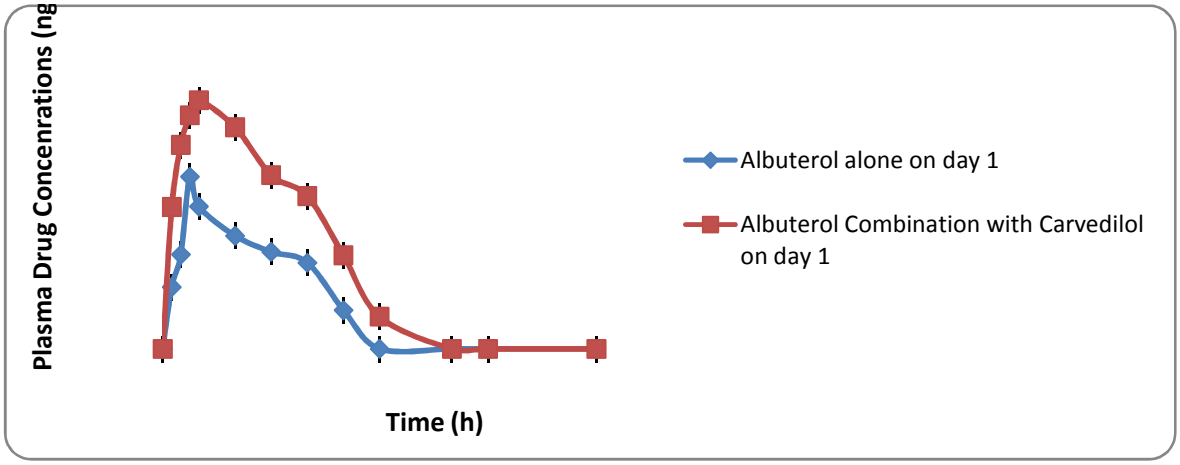

Figure 1: Mean ± S.E.M, plasma levels (ng/ml) of Albuterol alone and in Combination with Carvedilol on day 1

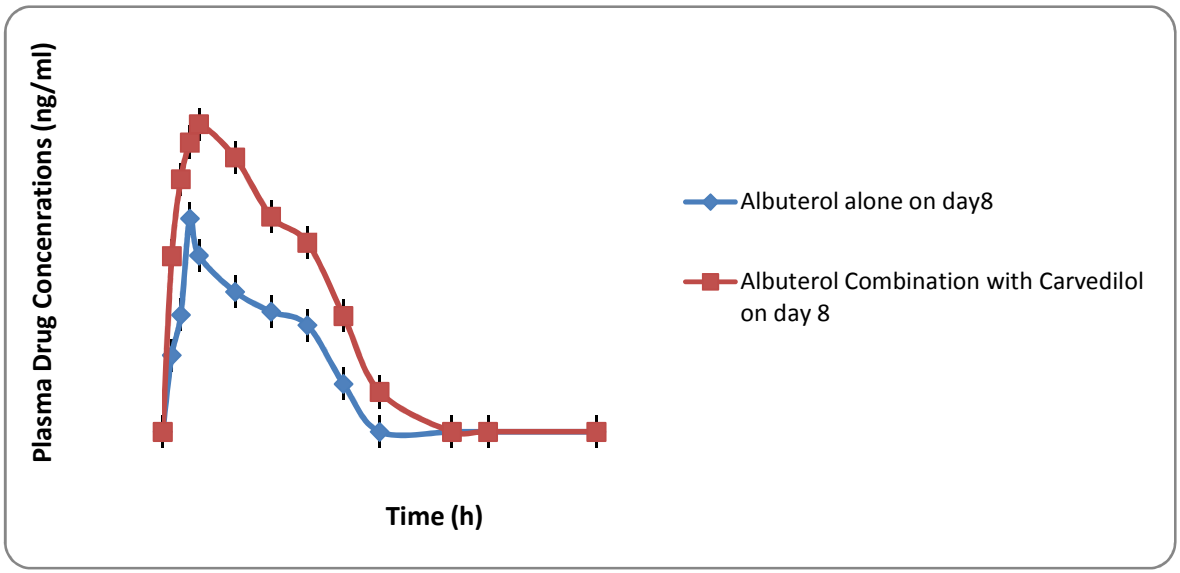

Figure 2: Mean ± S.E.M, plasma levels (ng/ml) of Albuterol alone and in Combination with Carvedilol on day 8

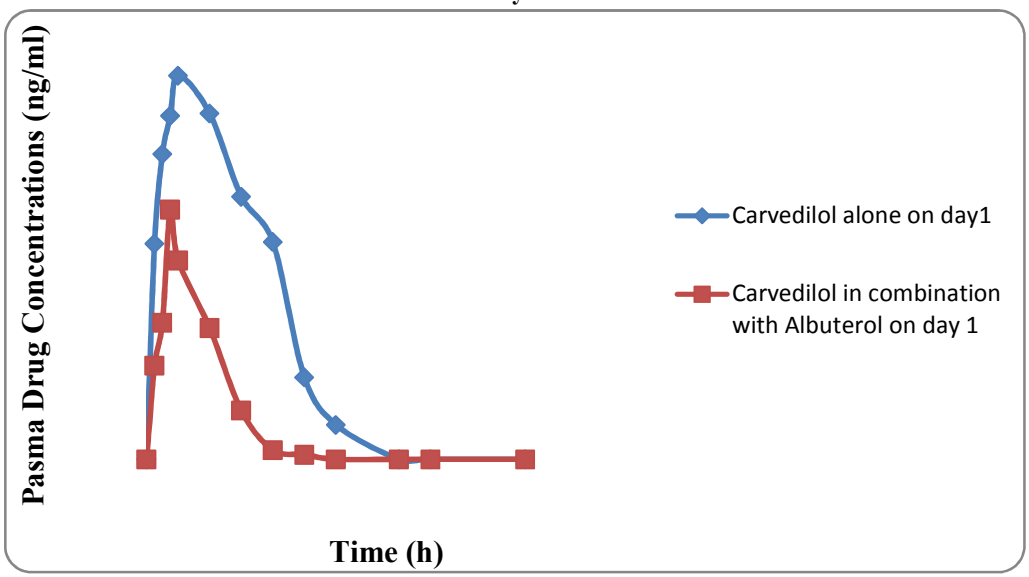

Figure 3: Mean ± S.E.M, plasma levels (ng/ml) of Carvedilol alone and in Combination with Albuterol on day 1

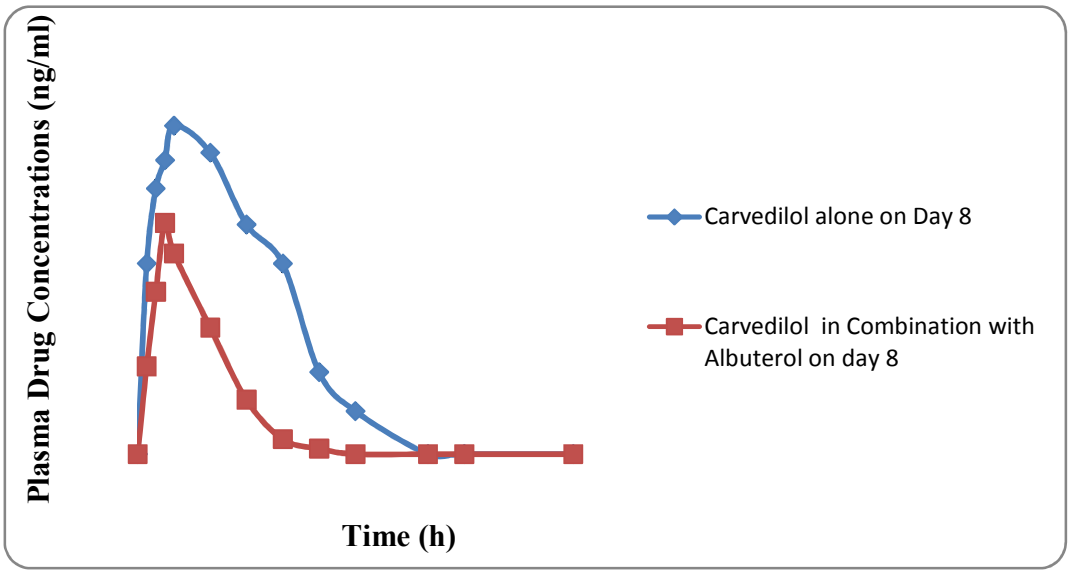

Figure 4: Mean ± S.E.M, plasma levels (ng/ml) of Carvedilol alone and in Combination with Albuterol on day 8

Table 1: Mean ± S.E.M, plasma levels (ng/ml) of Albuterol alone and in Combination with Carvedilol on day 1

Parameters	Albuterol alone	Albuterol in Combination with Carvedilol
C_{max} (ng/ml)	5.74±1.39	6.21±1.12 mean difference
$t_{max\ (h)}$	2±0	2±0
AUC_{o-t} (ng/ml/h)	172.45±7.74	182.37±7.32
AUC_{o-inf} (ng/ml/h)	348.82±8.50	375.15±8.67
$T_{1/2}$ (h)	6±0	6±0

Table 2: Mean ± S.E.M, plasma levels (µng/ml) of Albuterol alone and in Combination with Carvedilol on day 8

Parameters	Albuterol alone	Albuterol and in Combination with Carvedilol
C_{max} (ng/ml)	7.92±2.22	8.76±3.12
$t_{max\ (h)}$	2±0	2±0
AUC_{o-t} (ng/ml/h)	337.36±5.38	354.38±9.49
AUC_{o-inf} (ng/ml/h)	596.36±6.63	665.49±8.74
$T_{1/2}$ (h)	6±0	6±0

Table 3: Mean ± S.E.M, plasma levels (ng/ml) of Carvedilol alone and in Combination with Albuterol on day 1

Parameters	Carvedilol alone	Carvedilol in combination with albuterol
C_{max} (ng/ml)	66.26±3.56	67.83±3.14
$t_{max\ (h)}$	1.5	1.5
AUC_{o-t} (ng/ml/h)	566.49±5.16	587.61±5.87
AUC_{o-inf} (ng/ml/h)	986.33±4.37	992.54±6.52
$T_{1/2}$ (h)	5±0	5±0

Table 4: Mean ± S.E.M, plasma levels (ng/ml) of Carvedilol alone and in Combination with Albuterol on day 8

parameters	Carvedilol alone	Carvedilol in combination with albuterol
C_{max} (ng/ml)	69.26±3.96	71.83±3.76
$t_{max\ (h)}$	1.5	1.5
AUC_{o-t} (ng/ml/h)	571.47±5.98	597.61±5.76
AUC_{o-inf} (ng/ml/h)	991.45±4.54	998.54±6.76
$T_{1/2}$ (h)	5±0	5±0

DISCUSSION

In the present study, Albuterol is completely absorbed after oral administration with peak plasma concentration of 5.74±1.39ng/ml after 2hrs of dosing on day 1. In combination with Carvedilol on day 1, the peak plasma concentration of Albuterol 6.21±1.12ng/ml occurred 2hr after dosing. There was no significant increase in peak plasma concentration levels. Similarly Carvedilol is completely absorbed after oral administration with peak plasma concentration 66.26±3.56ng/ml occurred 1.5h after dosing on day 1 in combination with albuterol and Carvedilol on day 1. The peak plasma concentration of Carvedilol 91.83±3.02 ng/ml occurred 2h after dosing. There was no significant increase in the peak plasma concentration levels similarly on day 8 of Carvedilol alone and with combination of albuterol and Carvedilol on day 8. Peak plasma concentrations are 69.26±3.96ng/ml and 71.83±3.76ng/ml respectively similarly albuterol on day 8 and combination with Carvedilol concentrations are 7.92±2.22ng/ml and 8.76±3.12ng/ml respectively. There was no significant difference in peak plasma concentration on day 8 (P>0.05). There is no significant difference in AUC and t_{max} in both alone and combination treatment. The half-life was similar with alone and combination treatment on day 1 and day 8. All these changes were not statistically significant (P>0.05). All the results were showed in **Table (1-4).**

CONCLUSION

In the present study, based on the results obtained from kinetic study it is evident that the single dose of Carvedilol, albuterol individually and concomitantly treated rats did not show any bio statistically significant interactions in its pharmacokinetic parameters.

There is a bulk of evidence suggesting that Beta Blocker therapy is safe in COPD patients who need it for coexistent cardiovascular diseases. Epidemiological evidence suggested that its use reduces mortality and the risk of exacerbations in general terms; Benefits are less evident in those older or with more severe disease. Therapy should be attempted with selective beta−1 adrenergic blockade, but if necessary patients with concomitant stable mild to moderate COPD who do not have reversible airway obstruction can tolerate non-selective BB. Selective BB is recommended in patients with severe COPD or who have reversible airway obstruction. In these patients a close initial monitoring and management by physicians with experience is recommend. Observational evidence suggests that BB therapy does not increase the risk of in-hospital mortality or late mechanical ventilation during exacerbations; therefore it is not necessary to routinely withdraw them during these episodes.

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