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Pharmacokinetic Drug- Drug Interactions between Albuterol with Beta Blockers Timolol

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ABSTRACT

The present study was aimed to conduct to evaluate any possible pharmacokinetic interactions between albuterol and timolol. Study was conducted in Male Wistar rats; animals were divided in to three groups, Group I received albuterol alone in single dose / day in healthy rats. Group 2 received timolol alone in single dose / day in healthy rats. Group 3 received albuterol and timolol concomitant administration in healthy rats as a single dose / day. The treatment was given on day one and day 8 both alone albuterol and timolol concomitantly used both the drugs. There was no significant difference in both c_{max}, t_{max} and AUC_{0-t} and AUC_{o-inf} of albuterol alone and combination of timolol on day 1 and day 8 respectively. Based on the results obtained from kinetic study it is evident that the single dose of albuterol and timolol individually and concomitantly treated shows no statistically significant interactions in its pharmacokinetic parameters.

Keywords: Albuterol, timolol, pharmacokinetic interactions, AUC.

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INTRODUCTION

Drug interactions are a daily challenge for physicians and screening all potential interactions in the prescriptions has become very cumbersome and virtually impossible. [1] Most drugs have multiple pharmacologic effects in patients, especially the newer and more complex drugs that are marketed currently. Clinically significant drug interactions can occur when two or more drugs are taken in combination. [2] Drug-drug interaction is one cause of adverse reactions leading to an increase in risk of hospitalization and added health care costs. With the continuing increase in the list of drugs capable of interactions, detection of these interactions from prescriptions becomes more important to ensure effective patient care. [3] In recent years, serious drug interactions with some widely used drugs have emerged. We need to reevaluate the screening procedures for potential drug interactions and ensure that preventable drug interactions are identified and information regarding the same is

passed on to healthcare professionals. [4] A drug interaction can be defined as a measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance (including prescription and non-prescription drugs, food or alcohol). [5] Drug interactions are believed to occur in 3% to 7% of patients taking up to 10 medications, and in as many as 20% patients taking 10 to 20 medications. It is estimated that drug interactions cause up to 2.8% of all hospitalizations. [6]

Chronic obstructive pulmonary disease (COPD) is a prevalent condition affecting 6–10% of the general population and 11–18 % of the individuals older than 65 years. [7] Many patients with COPD have concomitant heart illnesses susceptible of treatment with betablocker agents (BB). In population studies, the prevalence of heart failure (HF) [8], coronary artery disease [9] and arterial hypertension [10], double those of the healthy control population and are usually higher than 20%. In fact, at least one of these heart conditions is present in 25–35% of the patients with COPD. [11] Moreover, supraventricular arrhythmias in some cases also susceptible to treatment with Beta Blockers are frequent in COPD as well. [12] Cardiovascular co morbidities occur even at the early stages of COPD, as it was shown in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study, in which the risk of cardiovascular disease, hypertension and diabetes was already increased in patients with chronic bronchitis without pulmonary function abnormalities yet (Global Initiative for Chronic Obstructive Lung Disease stage. [13] Albuterol is a bronchodilator that relaxes muscles in the airways and increases air flow to the lungs. Its inhalation is used to treat or prevent bronchospasm in people with reversible obstructive airway disease. It is also used to prevent exercise-induced bronchospasm.

Timolol is a medication used either by mouth or as eye drops. As eye drops it is used to treat increased pressure inside the eye such as in ocular hypertension and glaucoma. By mouth it is used for high blood pressure, chest pain due to insufficient blood flow to the heart, to prevent further complications after a heart attack, and to prevent migraines.

MATERIALS AND METHODS

Materials

Drugs and chemicals

Albuterol and timolol were procured from Aurobindo Pharma, Hyderabad as a gift sample. All HPLC grade solvents (methanol and water) were procured from Finar chemicals Ltd., Ahmadabad. All chemicals used were analytical grade.

Animal study

Male Wistar rats (weighing 200-220 g) were procured from the animal house CMR College of Pharmacy, Hyderabad. Animals were randomly divided into four 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 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: timolol alone in single dose / day in healthy rats.

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

Collection of Blood Samples

After administration of the drugs, blood samples of 0.5 ml 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 hours (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 3000 rpm 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 2.5 ml of ice-cold absolute ethanol for each 0.5 ml 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 1 min. After centrifugation (5000–6000 rpm for 10 min), 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, 250 × 4.6 mm, C_8 column with 5µm particle size and the mobile phase consisting of a mixture of Ammonium acetate (pH 5.0, 0.01 M) - Methanol in the ratio of 40:60 (v/v) with a flow rate of 1 ml/min. and the eluent was monitored at 254 nm. Brimonidine Tartrate used as internal standard. The retention times of Albuterol, timolol, Brimonidine Tartrate were found to be 8, 5.6 and 3 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, timolol 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, timolol in rat plasma is shown in Figures 1, 2, 3, and 4.

RESULTS AND DISCUSSION

In the present study, Albuterol is completely absorbed after oral administration with peak plasma concentration of 5.74 ± 0.39ng/ml after 2.5 hours of dosing on day 1. In combination with timolol on day 1, the peak plasma concentration of Albuterol 6.03 ± 1.12ng/ml occurred 2.5 hours after dosing. There was no significant increase in peak plasma concentration levels. Similarly timolol is completely absorbed after oral administration with peak plasma concentration 90.12 ± 3.03ng/ml occurred 2 hours after dosing on day 1 in combination with albuterol and timolol on day 1. The peak plasma concentration of timolol 91.83 ± 3.02ng/ml occurred 2 hours after dosing. There was no significant increase in the peak plasma concentration levels similarly on day 8 of timolol alone and with combination of albuterol and timolol on day 8.

Peak plasma concentrations are 94.12 ± 3.03ng/ml and 96.83 ± 3.02ng/ml respectively similarly albutrol on day 8 and combination with timolol concentrations are 7.92 ± 2.22ng/ml and 8.41 ± 3.1ng/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).

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

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

Parameters	Albuterol alone	Albuterol in Combination with timolol
C_{max} (ng/ml)	5.74 ± 0.39	6.03 ± 1.12
$t_{max\ (h)}$	2 ± 0	2 ± 0
AUC_{o-t} (ng/ml/h)	172.45 ± 0.74	176.37 ± 0.52
AUC_{o-inf} (ng/ml/h)	348.82 ± 2.50	376.15 ± 1.85
$T_{1/2}$ (h)	6 ± 0	6 ± 0

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

Parameters	Albuterol alone	Albuterol and in Combination with timolol
C_{max} (ng/ml)	7.92 ± 2.22	8.41 ± 3.1
$t_{max\ (h)}$	2.5 ± 0	2.5 ± 0
AUC_{o-t} (ng/ml/h)	337.36 ± 5.38	343.38 ± 9.49
AUC_{o-inf} (ng/ml/h)	596.36 ± 6.63	613.49 ± 8.74
$T_{1/2}$ (h)	6 ± 0	6 ± 0

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

Parameters	Timolol alone	Timolol in combination with albuterol
C_{max} (ng/ml)	90.12 ± 3.03	91.83 ± 3.02
$t_{max\ (h)}$	2 ± 0	2 ± 0
AUC_{o-t} (ng/ml/h)	833.49 ± 5.16	841.62 ± 7.20
AUC_{o-inf} (ng/ml/h)	1252.33 ± 4.37	1262.16 ± 6.52
$T_{1/2}$ (h)	5 ± 0	5 ± 0

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

Parameters	Timolol alone	Timolol in combination with albuterol
C_{max} (ng/ml)	94.12 ± 3.03	96.83 ± 3.02
$t_{max\ (h)}$	2 ± 0	2 ± 0
AUC_{o-t} (ng/ml/h)	935.29 ± 2.01	971.32 ± 3.22
AUC_{o-inf} (ng/ml/h)	1451.32 ± 3.37	1462.13 ± 2.52
$T_{1/2}$ (h)	5 ± 0	5 ± 0

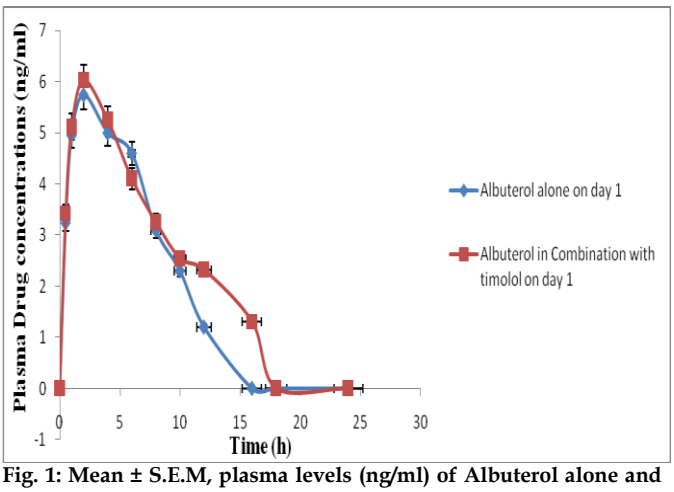

Fig. 1: Mean ± S.E.M, plasma levels (ng/ml) of Albuterol alone and in Combination with timolol on day 1

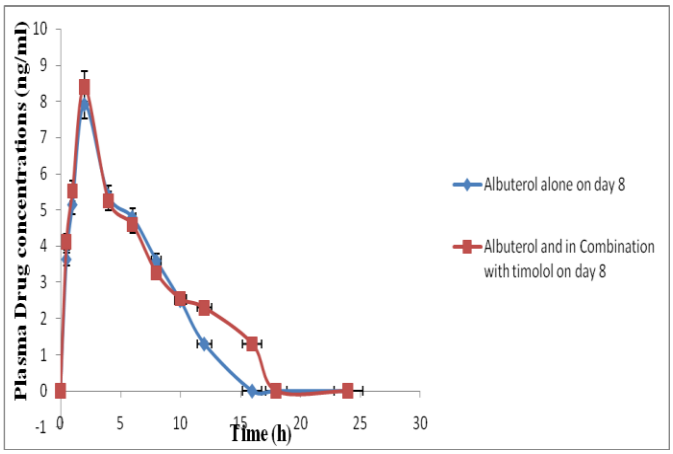

Fig. 2: Mean ± S.E.M, plasma levels (ng/ml) of Albuterol alone and in Combination with timolol on day 8

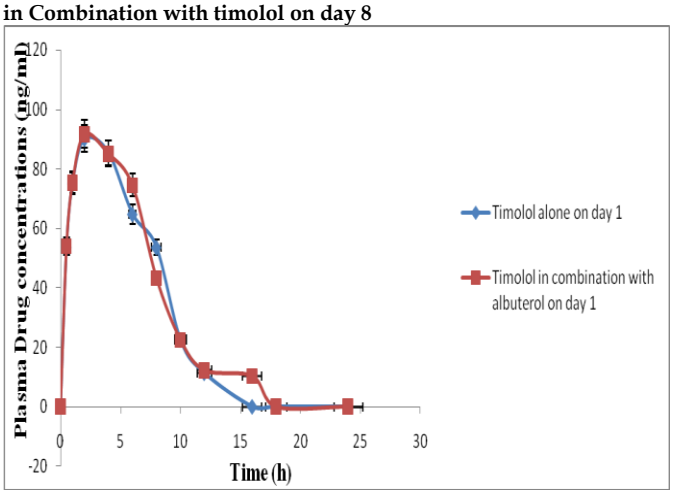

Fig. 3: Mean ± S.E.M, plasma levels (ng/ml) of timolol alone and in Combination with Albuterol on day 1

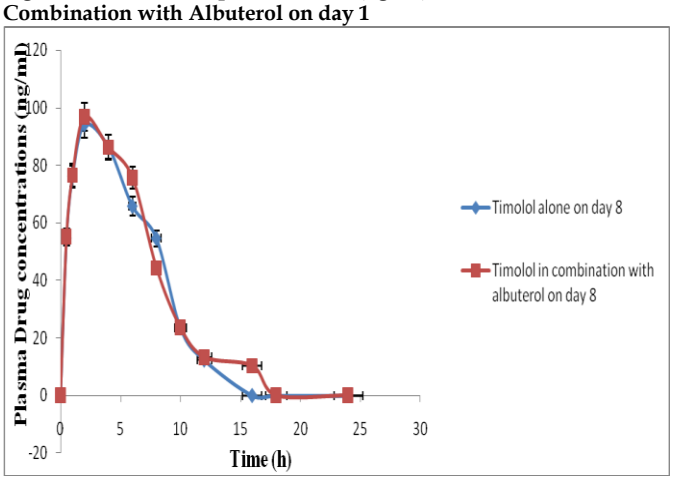

Fig. 4: Mean ± S.E.M, plasma levels (ng/ml) of timolol alone and in Combination with Albuterol on day 8

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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