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Effect of Triple Combination of Nebivolol, Lansoprazole and Cefixime on Pharmacokinetics of Nebivolol in Hypertensive Patients

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ABSTRACT

The present study was carried out to find out the pharmacokinetic drug interaction of lansoprazole and cefixime on nebivolol plasma concentrations following coadministration of single oral doses in hypertensive patients. Therapeutic dose of nebivolol alone and triple combination of nebivolol, lansoprazole and cefixime was administered to seperate group of hypertensive patients. Serial blood samples were collected at pre-dose (0.0) to 36 h post-dose to characterize the pharmacokinetic parameters. The plasma nebivolol concentrations were estimated by a sensitive liquid chromatographic mass spectrometry (LC-MS) method. Mean (SD) of AUC_{0-t} (ng.h/mL) and $AUC_{0-\infty}$ (ng.h/mL) for nebivolol given as a triple combination versus nebivolol alone is 38.62 (8.81) vs. 17.29 (4.60) and 47.98 (10.22) vs. 24.42 (5.08) respectively. Corresponding values for C_{max} (ng/mL) is 5.99 (1.07) vs. 3.09 (0.37). Triple combination of these drugs significantly increased the bioavailability of nebivolol in hypertensive patients than nebivolol alone. Thus there observed to be a pharmacokinetic interaction when nebivilol is administered in combination with lansoprazole and cefixime. Hence, the combination is contraindicated or used with caution in a clinical situation.

Keywords: *Nebivolol, lansoprazole, cefixime, bioavailability, LC-MS method.*

INTRODUCTION

Hypertension or elevated blood pressure is one of the major cardiovascular complications. Evidences suggest that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischemic heart disease by 21% and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease [1]. There are many classes of antihypertensives, which lower blood pressure by different means, among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers, and the angiotensin II receptor antagonists (ARBs). Angiotensin II Receptor type 1 antagonists have been widely used in the treatment of disease like Hypertension, Heart failure, Myocardial infarction and Diabetic nephropathy [2, 3].

β-blockers constitute one of the most frequently prescribed groups of cardiovascular drugs. They are competitive antagonists at β-adrenergic receptor sites and are used in the management of cardiovascular disorders, such as hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction. Nebivolol is a highly selective β1-blocker with nitric oxide mediated vasodilatory actions and beneficial effects on vascular endothelial function [4-6].

In some unavoidable dependent conditions of patients wherein the simultaneous administration of antihypertensive agents like nebivolol with proton-pump inhibitors like lansoprazole, antibiotic drugs like cefixime for the effective management of the patient condition may be required. Hence there is a possibility for the drug-drug interaction in those patients prescribed with above drug combination. As there is lack of pharmacokinetic drug interaction data, we have undertaken this study to evaluate the effect of lansoprazole and cefixime coadministration on the pharmacokinetics of nebivolol in hypertensive patients.

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MATERIALS AND METHODS

Nebivolol hydrochloride tablets 5mg (Aristo Pharmaceuticals, India), lansoprazole capsules 30mg (Lanzol 30, Cipla Ltd, India) and Cefixime Tablets IP 200mg (Elite Pharma, India) were used for the study. Water, HPLC grade methanol, ammonium formate of analytical grade, ethyl acetate, dichloro methane were purchased from Qualigens fine chemicals, Mumbai, India.

Liquid Chromatographic conditions:

Shimadzu UFLC system consisting of Binary solvent Pump (LC-20AD), Auto sampler (SIL-HTC), Degasser (DGU-20A3) and Column oven (CTO-10ASVP) was used for setting the reverse-phase liquid chromatographic conditions. The separation of nebviolol and tamsulosin (ISTD) was performed on Hypersil BDS C18 (50mm×4.6mm (length inner diameter), with 3 µm particle size) and was maintained at 30°C in column oven. The mobile phase consists of 2.5mM ammonium formate and methanol in 25:75 (v/v) ratio. For isocratic elution, the flow rate of the mobile phase was kept at 0.4 mL/min. The total chromatographic run time was 2.5 min. The auto sampler temperature was maintained at 15°C.

Mass spectrometric conditions:

Ionization and detection of nebivolol and tamsulosin (ISTD) was carried out on a triple quadrupole mass spectrometer. ABSCIEX, API3200 equipped with electro spray ionization and operating in positive ion mode. Quantization was performed using multiple reaction monitoring (MRM) mode to monitor parent → product ion (m/z) transitions for nebivolol 406.0 → 151.0 and 409.1 → 228.1 for tamsulosin (ISTD).

Standard stock, calibration standards and quality control sample preparation:

The standard stock solution of 1 mg/mL of nebviolol and tamsulosin (ISTD) was prepared by dissolving requisite amount in methanol. Calibration standards and quality control (QC) samples were prepared by spiking (1% total volume of blank plasma) blank plasma with stock solution. Calibration curve standards were made at 0.51, 1.01, 2.03, 6.00 , 8.00, 20.01, 40.02 and 50.03 ng/mL respectively while quality control samples were prepared at three levels, viz. 37.00 ng/mL (HQC, high quality control), 20.17 ng/mL

(MQC, middle quality control), 1.51 ng/mL (LQC low quality control).

Protocol for sample preparation:

Prior to analysis, all frozen subjects samples, calibration standards and quality control samples were thawed and allowed to equilibrate at room temperature. To an aliquot of 500 µL of spiked plasma sample, add 50 µL internal standard (tamsulosin) and 50 µL of ammonia solution and vortexes. To these samples, 2.5 mL of extraction solvent (Ethyl acetate : Dichloromethane 80:20, v/v) was added and samples were extracted on extractor at 2500rpm for 10min. centrifugation of the samples was done at 4000rpm for 10 min at 10°C. Supernant was separated and evaporated to dryness under nitrogen at 50°C and 15 psi for 15 min. The dried samples were reconstituted with 750 µL of mobile phase and inject 10µL of sample into chromatographic system.

Study Design:

Hypertensive patients were randomly distributed into two groups of eight patients each. After collection of predose (0.0 h) blood sample, single dose treatments were administered orally in the following order.

Group I - Nebivolol hydrochloride tablet 5mg
Group II - Triple combination of nebivolol hydrochloride tablet 5 mg, lansoprazole capsules 30mg and cefixime tablet 200mg

Collection and analysis of blood samples:

Blood sample of approximately 2.5 mL was collected from each patient at 0.0 (predose), 0.17, 0.5, 1.5, 6, 12, 18, 24 and 36 h time intervals in to heparinized tubes after each treatment. Plasma was obtained by immediate centrifuged at 3000 rpm for 10 minutes at room temperature and stored at 4^{0}C until analysis. The study samples were analyzed for nebivolol concentrations using LC-MS method. Prior approval of the study protocol was obtained by Institutional Human Ethical Committee.

Pharmacokinetic analysis:

The pharmacokinetic parameters of nebivolol were computed using a sophisticated tool known as WinNonlin, Version 4.1 (Pharsight Corporation, USA) and the parameters includes area under the plasma concentration time curve from time zero to the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration time curve from zero to time infinity ($AUC_{0-\infty}$), maximum measured plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), terminal phase elimination rate constant (K_{el}), and half-life ($t_{1/2}$).

Data and statistical analysis:

The data was expressed as mean ± standard deviation (SD). The significance was determined by applying student's paired 't'test. A value of $P < 0.05$ was considered statistically significant.

Collection and analysis of blood samples:

After administration of the drug, blood samples of 2.5 ml were drawn into heparinized tubes. The plasma was obtained by immediate centrifugation at 3000 rpm for 10 minutes at room temperature. All samples were stored at 4^{0}C until analysis. The study samples were analyzed for serum nebivolol concentrations using LC-MS method. The protocol was approved by Institutional Human Ethical Committee.

RESULTS AND DISCUSSION

The mean plasma concentration time profile following single oral dose of nebivolol alone and in combination with lansoprazole in hypertensive patients were shown in **Fig. 1**. The pharmacokinetic (PK) parameters of nebivolol were presented in **Table 1**. From the PK parameters, it is observed that the rate (C_{max}) and extent of exposure (AUC_{0-t} and $AUC_{0-\infty}$)was significantly increased with a relative decrease in the time to reach peak plasma concentration (t_{max}) when nebivolol was used in combination with lansoprazole, cefixime together than nebivolol alone. On the other hand, there was slight decrease elimination parameter, K_{el} with triple combination than nebivolol alone, but the decrease is not significant.

Triple combination of lansoprazole, cefixime and nebivolol in hypertensive patients, percentage increase of nebivolol in comparison with the nebivolol alone treated group for the various PK parameters is AUC_{0-t} (2.2%), $AUC_{0-\infty}$ (2.0%), C_{max} (1.9%) and $t_{1/2}$ (1.7%) with a rapid reduction in t_{max} (3.0%) and minor decrease in K_{el} (1.9%). Both the drugs lansoprazole and cefixime increased the rate and extent of exposure of nebivolol resulting in increased nebivolol plasma availability thereby producing pronounced antihypertensive effect for a extended period of time. This indicates that this combination must be avoided or taken with caution in clinical conditions.

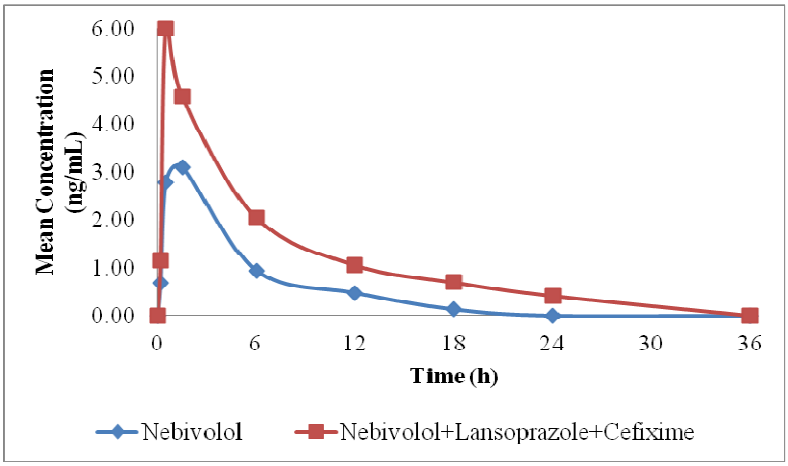

Fig. 1: Plasma concentration of Nebivolol following single dose of Nebivolol alone and triple combination of Nebivolol, Lansoprazole, Cefixime in Hypertensive patients (N=8)

Table No.1: Pharmacokinetic parameters of Nebivolol in presence of triple combination of Lansoprazole, Cefixime and Nebivolol in Hypertensive patients (n=8)

PK Parameter	Nebivolol	Nebivolol + Lansoprazole Cefixime
AUC_{0-t} (ng.h/mL)	17.29±4.60	38.62±8.81**
$AUC_{0-\infty}$ (ng.h/mL)	24.42±5.08	47.98±10.22**
C_{max} (ng/mL)	3.09±0.37	5.99±1.07*
t_{max} (h)	1.50±0.00	0.5±0.00**
K_{el} (h^{-1})	0.13±0.05	0.07±0.03
$t_{1/2}$(h)	6.60±1.17	10.90±3.46

*Significant at P<0.05, **Significant at P<0.01, compared to nebivolol control; Values were represented as mean ± SD.

CONCLUSION

Simultaneous administration of drugs like nebivolol, lansoprazole and cefixime in the treatment of hypertension requires the attention of clinical health care professionals as there is a significant change in the pharmacokinetics of primary drug (nebivolol) during this investigation. If such combination is mandatory in certain clinical situations, it is advisable to alter the dosage regimen of the primary drug (nebivolol).

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Conflict of interest: The authors have declared that no conflict of interest exists.

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