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EFFECT OF CEFIXIME ON PHARMACOKINETICS OF NEBIVOLOL IN HYPERTENSIVE PATIENTS

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ABSTRACT: The present study was carried out to assess the pharmacokinetic drug interaction between nebivolol and cefixime following single oral dose administration in hypertensive patients. Therapeutic dose of nebivolol alone and combination with cefixime were administered to a separate group of hypertensive patients. Serial blood samples were collected at pre-dose (0.0) to 48 h post-dose following each treatment to characterize the pharmacokinetic parameters. The plasma nebivolol concentrations were estimated by a sensitive liquid chromatographic mass spectrometry (LC-MS) method. Mean (SD) of $AUC_{0\text{-}t}$ (ng.h/mL) and $AUC_{0\text{–}\infty}$ (ng.h/mL) for nebivolol given as a combination versus nebivolol alone is 39.24 (6.96) vs. 17.29 (4.60) and 45.30 (6.70) vs. 24.42 (5.08) respectively. Corresponding values for C_{max} (ng/mL) is 2.98 (0.47) vs. 3.09 (0.37). Cefixime significantly increased the extent of exposure of nebivolol when used in combination. There was minor change in the peak exposure and elimination parameters. The results indicate that there observed to be a pharmacokinetic interaction when nebivolol is administered in combination with cefixime. Hence, the combination is contraindicated or used with caution in a clinical situation.

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].

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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].

Analytical methods employed for the determination of drugs and metabolites in biological matrices such as urine, plasma and serum are essential throughout drug discovery and development. It is well-known that analytical techniques are constantly undergoing change and improvements and each analytical method has its own characteristics which may vary from analyte to analyte at different conditions. As the drug continues through development, the decisions become more critical therefore, the bio-analytical methods that produce the data should be accurate [7].

Liquid chromatography-mass spectrometry (LC-MS) in an analytical chemistry technique that combines the physical separation of an analyte (drug) and with the help of the mass analysis of drug (using mass spectrometry) is a very high sensitivity and specific tool for bio-analytical requirements in clinical trial research [8-9].

In some unavoidable dependent conditions of patients wherein the simultaneous administration of antihypertensive agents like nebivolol with 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 drugs. As there is lack of pharmacokinetic drug interaction data, we have undertaken this study to evaluate the effect of cefixime on the pharmacokinetics of nebivolol in hypertensive patients.

MATERIALS AND METHODS: Nebivolol hydrochloride tablets 5mg (Aristo Pharmaceuticals, 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 Nebviolol 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 nebviolol 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 hr) blood sample, single dose treatments were administered orally in the following order. Group I — Nebivolol hydrochloride tablet 5mg

Group II — Combination of nebivolol tablet 20mg 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 48 hr 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 40C 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.

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

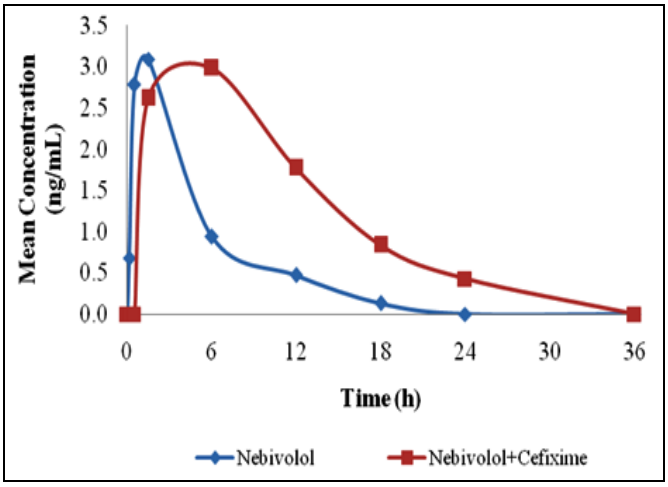

FIGURE 1: PLASMA CONCENTRATION (NG/ML) OF NEBIVOLOL FOLLOWING SINGLE DOSE OF NEBIVOLOL ALONE AND COMBINATION WITH CEFIXIME IN HYPERTENSIVE PATIENTS (N=8)

TABLE 1: PHARMACOKINETIC PARAMETERS OF NEBIVOLOL IN PRESENCE OF CEFIXIME IN HYPERTENSIVE PATIENTS (N=8)

PK Parameter	Nebivolol	Nebivolol + Cefixime
AUC_{0-t} (ng.h/mL)	17.29±4.60	39.24±6.96**
$AUC_{0-\infty}$ (ng.h/mL)	24.42±5.08	45.30±6.70**
C_{max} (ng/mL)	3.09±0.37	2.98±0.47
t_{max} (h)	1.50±0.00	6.00±0.00**
K_{el} (h^{-1})	0.13±0.05	0.10±0.01
$t_{1/2}$(h)	6.60±1.17	7.00±0.72

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

In single dose combination with cefixime in hypertensive patients, percentage increase of nebivolol in comparison with the nebivolol alone treated group for the various PK parameters is AUC_{0-t} (2.3%), $AUC_{0-\infty}$ (1.9%), t_{max} (3%), $t_{1/2}$ (1.1%) with a relatively minor decrease in C_{max} (0.9%), and K_{el} (0.90%). Cefixime increased the extent of exposure of nebivolol resulting in increased nebivolol plasma availability thereby producing antihypertensive effect for a extended period of time. This indicates that this combination must be avoided or taken with caution in clinical conditions.

CONCLUSION: Simultaneous administration of drugs like nebivolol 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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