Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Scholars Research Library

Annals of Biological Research, 2013, 4 (10):6-10
(http://scholarsresearchlibrary.com/archive.html)

Annals of Biological Research
Scholars Research Library
ISSN 0976-1233
CODEN (USA): ABRNBW

Effect of lansoprazole on pharmacokinetics of nebivolol in hypertensive patients

Venkateswarlu Bollam[1*], Jayaprakash Dodle[2] and Ravindernath Anisetti[3]

[1]University College of Technology, Osmania University, Hyderabad, Andhra Pradesh, India
[2]Department of Chemical Engineering, University College of Technology, Osmania University Hyderabad, Andhra Pradesh, India
[3]Department of Biotechnology & Pharmacy, University College of technology, Osmania University Hyderabad, Andhra Pradesh, India

---

ABSTRACT

The present study was carried out to assess the pharmacokinetic drug interaction between nebivolol and lansoprazole following single oral dose administration in hypertensive patients. Therapeutic dose of nebivolol alone and combination with lansoprazole were administered to a separate group of hypertensive patients. Serial blood samples were collected at pre-dose (0.0) to 36 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-t} (ng.h/mL) and $AUC_{0-\infty}$ (ng.h/mL) for nebivolol given as a combination versus nebivolol alone is 34.08 (6.67) vs. 17.29 (4.60) and 43.36 (10.61) vs. 24.42 (5.08) respectively. Corresponding values for C_{max} (ng/mL) is 6.37 (0.89) vs. 3.09 (0.37). Lansoprazole significantly increased the peak and extent of exposure of nebivolol when used in combination. There was minor change in the elimination parameters. The results indicate that there observed to be a pharmacokinetic interaction when nebivolol is administered in combination with lansoprazole. Hence, the combination is contraindicated or used with caution in a clinical situation.

Keywords: Nebivolol, lansoprazole, pharmacokinetic and 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].

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 [3].

Lansoprazole, chemically known as 2-[[3-methyl- 4-(2,2,2-trifluoroethoxy) pyridin-2-yl] methylsulfinyl] -1H-benzimidazole. It is a member of the proton-pump-inhibitor class of gastric acid inhibitory agents, effectively raises intragastric pH and is indicated for the short-term treatment of active erosive reflux esophagitis, gastric ulcer, duodenal ulcer, and nonerosive gastroesophageal reflux disease. As a proton-pump inhibitor, it is also a necessary component of dual- and triple therapy regimens for the eradication of Helicobacter pylori infection. The latest FDA-approved labeling for lansoprazole includes the indication of healing and risk reduction in nonsteroidal anti-inflammatory drug-associated gastric ulcers [4-6].

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately at 1.7 h after oral dosing, and relatively complete with absolute bioavailability over 80%. There is no significant food effect if the drug is given before meals. It is 97% bound to plasma proteins, and extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (hydroxylated sulfinyl and sulfone derivatives of lansoprazole). Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid pump inhibitor, in that it blocks the final step of acid production [7-9].

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. Liquid chromatography-mass spectrometry (LC-MS) in an analytical chemistry technique that combines the physical separation of a 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 [10-11].

In some unavoidable dependent conditions of patients wherein the simultaneous administration of antihypertensive agents like nebivolol and proton pump inhibitors like lansoprazole 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. Since the lack of pharmacokinetic drug interaction data, we have undertaken this study to evaluate the effect of lansoprazole on the pharmacokinetics of nebivolol in hypertensive patients.

MATERIALS AND METHODS

Nebivolol hydrochloride tablets 5mg (Aristo Pharmaceuticals, India), and lansoprazole capsules 30mg (Lanzol 30, Cipla Ltd, 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 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 lansoprazole capsules 30mg.

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 4^0C 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 4^0C 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 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 lansoprazole 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)

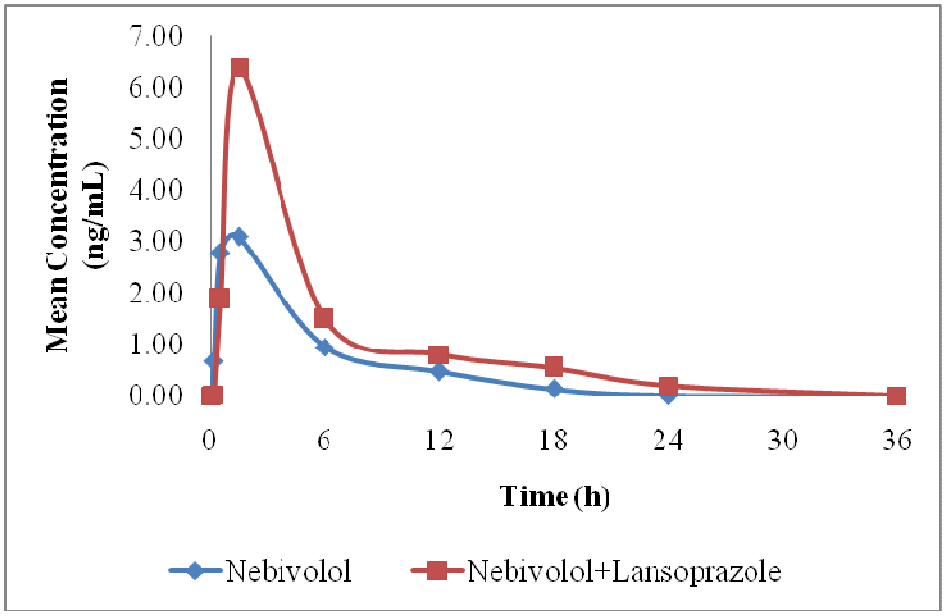

Table 1: Pharmacokinetic parameters of nebivolol in presence of lansoprazole in hypertensive patients (n=8)

PK Parameter	Nebivolol	Nebivolol + lansoprazole
AUC_{0-t} (ng.h/mL)	17.29±4.60	34.08±6.67**
$AUC_{0-\infty}$ (ng.h/mL)	24.42±5.08	43.36±10.61**
C_{max} (ng/mL)	3.09±0.37	6.37±0.89*
t_{max} (h)	1.50±0.00	1.5±0.00
K_{el} (h^{-1})	0.13±0.05	0.08±0.06
$t_{1/2}$(h)	6.60±1.17	11.92±7.09

**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 lansoprazole in hypertensive patients, percentage increase of nebivolol in comparison with the nebivolol alone treated group for the various PK parameters is AUC_{0-t} (2.0%), $AUC_{0-\infty}$ (1.8%), C_{max} (2.1%) and $t_{1/2}$ (1.8%) with a relatively minor decrease in K_{el} (1.6%). Lansoprazole 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.

CONCLUSION

Simultaneous administration of drugs like nebivolol and lansoprazole 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).

Acknowledgements
The authors thank all the clinical site staff and the study subjects for their contribution to this study.

REFERENCES

[1] M. Law, N. Wald, J. Morris. *Health Technol Assess.*, **2003**, **7** (31): 1–94.

[2] N. Siddiqui, A. Husain, L. Chaudhary, M.S. Alam, M. Mitra, P.S. Bhasin. *J Applied Pharm Sci*., **2011,** 1(4): 12-19.
[3] P.S. Selvan, K.V. Gowda, U. Mandal, W.D. Solomon, T.K. Pal. *J Chromatogr B Analyt Technol Biomed Life Sci*., **2007**, 858(1-2): 143-50.
[4] R.J. Brummer, B.J. Geerling, R.W. Stockbrugger. *Dig Dis Sci*., **1997**; 42: 2132–2137.
[5] D.S. Threlkeld. Gastrointestinal Drugs, Proton Pump Inhibitors. *In Facts and Comparisons Drug Information*. St. Louis, MO, **1998**; 305r.
[6] K.G. Tolman, S.W. Sanders, K.N. Buchi, M.D. Karol, D.E. Jennings, G.L. Ringham. *J Clin Gastroenterol.*, **1997**, 24(2): 65-70.
[7] A. Fitton, L. Wiseman. *Drugs.*, **1996**, 51: 460-482.
[8] A.J. Matheson, B. Jarvis. *Drugs.*, **2001**, 61: 1801-1833.
[9] R.L. Bown. *Int. J. Clin. Pract.*, **2002**, 56: 132-139.
[10] R.E. Ardrey. Liquid Chromatography-Mass Spectrometry: An Introduction, *John Wiley & Sons, Ltd*, London, **2003**.
[11] W.A. Korfmacher: *Drug Discovery Today*., **2005**, 10(20): 1357-1367.