Original Article

Pharmacokinetic and pharmacodynamic correlation of plasma concentrations and blood pressure in hypertensive patients: A study

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ABSTRACT

Objective: The aim of this study was to determine the correlation between the pharmacokinetic (PK) parameter (plasma concentration) and pharmacodynamic (PD) parameter (blood pressure [BP]) in hypertensive patients on metoprolol therapy.

Materials and Methods: High-performance liquid chromatography (HPLC) method for the measurement of plasma concentrations was developed and validated, following which the Ethical Committee approval was obtained. Patients admitted with hypertension and above 18 years of age were randomized into two groups based on the time of administration of metoprolol. Patients for whom metoprolol therapy was contraindicated were excluded from the study.

Results: One hundred and six patients were enrolled in the study; patients with 61–70 years formed majority, 51.8% of males were associated with hypertension compared to 48.2% of the females. Patients receiving morning dose of the drug showed higher plasma concentrations in comparison with evening dose. PK and PD correlation was carried out and correlation coefficient "R^2" was calculated by the formula $y = mx + c$. For systolic BP of morning administration, R^2 for peak concentration was found to be 0.913 and R^2 for trough concentration was found to be 0.903. R^2 value for diastolic BP of morning administration was found to be 0.873 for peak concentration and 0.969 for trough concentration. Systolic BP of evening exhibited R^2 value of 0.986 and 0.955 for peak and trough concentrations, respectively. Diastolic BP of evening showed R^2 value of 0.931 and 0.896 for peak and trough concentrations. Statistical analysis was done using Pearson's correlation test, and it was observed that there is a significant correlation ($P < 0.001$) between the plasma concentrations and BP.

Conclusion: The PK and PD parameters are at par with each other. It can be concluded that there is a significant correlation between the BP and plasma concentrations. This can be considered as the preliminary finding to ascertain the various PK parameters to optimize the dosing schedule for hypertensive patients.

Key words: Hypertension, metoprolol, pharmacodynamics, pharmacokinetics

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INTRODUCTION

Temporal variations of effect and disposition of drugs can be attributed to endogenous biologic rhythms. The circadian changes of more than one hundred different compounds were documented very early, including sustained-release preparations. Kinetic studies related to the patient, the drug, and/or its environment depend on a number of variables, namely age, gender, diseases, and physiopathological conditions. These factors have been extensively studied and are regularly mentioned. However, if the time of administration of drugs is taken into account to determine the relationships between time and concentration of drugs in usual pharmacokinetic (PK) studies, the possible influence of biological clock time hour of drug administration can be established.[1,2]

Dose-concentration relationships (PK) and dose-effect relationships (pharmacodynamics [PD]) can be positively linked to facilitate the description and prediction of the time course of the drug effects resulting from a dosing regimen. PK/PD correlations in clinical therapy can provide a more rational basis of patient-specific dosage individualization and may directly applied pharmacotherapy to a higher level of performance.

Hypertension is a common chronic condition affecting a large population of human adults. This condition is an important risk factor for strokes, heart attacks, and other vascular and renal diseases.[3] Blood pressure (BP) varies according to the time of the day. Both in healthy and hypertensive participants, the existence of circadian rhythms is confirmed in BP.[4] BP rises rapidly in the morning upon awakening, this elevation is called morning surge, and it is thought to be brought on by arousal due to increased sympathetic activity,[4-6] and increased activity of renin-angiotensin system which stimulates secretion of angiotensin II, one of the most powerful vasoconstrictors.

The effects of time of dosing on the PD effects of long-acting, once-daily antihypertensive drugs are an important consideration for antihypertensive therapy plan. It is an incorrect assumption that a drug administered in the morning will have the same antihypertensive effect as dosed in the evening. Studies using ambulatory monitoring of BP and heart rate have shown that altering the dosing time of antihypertensive agents may have a clinically meaningful effect on circadian BP.

Beta-blockers are the most ancient and well accepted for more than four decades of use in the treatment of hypertension.[7,8] Among the most widely used agents within the class are the β1-selective compounds such a metoprolol. Metoprolol succinate (controlled, long-acting release) formulation when given once daily[9,10] improves the patient adherence and outcome as a result of improved compliance.

MATERIALS AND METHODS

A prospective, randomized, cohort study was carried out at a tertiary care hospital of South India to establish a PK/PD relationship between the plasma concentrations and therapeutic effects of metoprolol to optimize the dosing schedule based on the administration time.

Source of data

Data were collected from prospective inpatients case sheets, laboratory reports, and interviewing patients who were suffering from hypertension and were admitted to the medicine wards in the hospital.

Inclusion criteria

Patients above 18 years of age who were admitted to the hospital who suffered from hypertension, ischemic heart disease, and coronary artery disease, and who were on metoprolol therapy were included in the study.

Exclusion criteria

Patients for whom metoprolol therapy was contraindicated, namely asthmatics, severe peripheral vascular disease, and patients with congestive cardiac failure. Outpatients, pregnant and lactating patients, and pediatrics were not considered for inclusion.

Method of data collection and sampling

At the outset, patients' case notes were analyzed. Based on the diagnosis, the patients were screened out as per the inclusion and exclusion criteria, and patients suffering from hypertension were considered. Informed consent was obtained after explaining to them about the study with the help of patient information sheet. In case where patients were not able to give the consent, same was obtained from their nearest relatives. Patients willing to participate and who gave their consent voluntarily were recruited.

Randomization was carried out using randomization tables, and all patients were either included in the

group of morning administration of the drug or in the group of evening administration.

The patients were administered with once daily metoprolol therapy. Plasma samples were collected from these patients only after steady state concentration was achieved.[11] $t_{1/2}$ of metoprolol is 3–7 h and the time required to reach the steady state concentration would be 15–35 h. The samples were drawn after 24 h of initiation of the treatment.

Blood samples were collected from patients who were treated with metoprolol at different time intervals including peak and trough concentrations after steady state was achieved. Sampling for peak concentration was carried out after 2–3 h following the administration of the dose.

The blood samples for trough concentrations were withdrawn just before the administration of the next dose. Two milliliter of blood each for peak and trough concentration was withdrawn from every individual patient involved in the study. The withdrawn blood samples were immediately transferred to the blood collecting tubes, i.e., precoated ethylenediaminetetraacetic acid (EDTA) Vacutainers (2 ml) and were suitably labeled. EDTA was used as the anticoagulant agent for obtaining the plasma samples.

The collected blood samples were then subjected to centrifugation to separate the plasma from the blood components. Centrifugation was carried out for a period of 25 min. The plasma which appeared as a clear supernatant liquid was transferred into the Eppendorf tubes (2 ml), and these plasma containing tubes were stored at a temperature of −20°C until it was subjected to analytical estimation by high-performance liquid chromatography (HPLC).[11,12] The stored plasma samples were subjected to analytical estimation by HPLC. Prior to the preparation of these plasma samples for estimation, they were freeze-thawed and then used.

Estimation of the metoprolol concentration in hypertensive patients was carried out using Grace C_{18} ODS 2, 250 mm × 4.6 mm, reversed-phase column packed with 5 µm spherical ODS packing. Shimadzu SPD 10 AT VP variable wavelength detector and injection loop of 50 µl were used and metoprolol detection was carried out at 262 nm. The concentration of metoprolol in the hypertensive patients was obtained by extrapolation of the peak area from the standard calibration curve ($y = mx + c$; $R^2 = 0.9908$) of metoprolol.

RESULTS AND DISCUSSION

A total number of patients included in the study were 106. All the patients were randomized into morning administration or evening administration group, 58 patients formed the morning administration group, and 48 patients were enrolled in the evening administration group. The drug metoprolol succinate (25 and 50 mg) was administered once daily at 8 am and 8 pm, respectively. Blood was drawn for the analysis of peak and trough concentration after the steady state was achieved. Chromatographic analysis was carried out to ascertain the plasma concentration of the drug. Clinical measurement of BP was done after every 30 min till 2 h. PK and PD correlations were drawn from the obtained data.

Majority of the patients were males (51.8%) than female (48.2%) counterparts, this difference of gender distribution can be attributed to certain habits like smoking, more commonly prevalent with males. It was observed that patients ranging between 61 and 70 years of age formed the preponderance. This accounts for more number of cardiovascular problems in geriatrics. If hypertension at this age is not effectively controlled then it can lead to various cardiovascular complications. Similar findings stating geriatric population being at risk of developing cardiovascular complications due to age and ineffective control of BP have been reported previously.

Patients suffered from various comorbidities, of which diabetes mellitus was observed to be present in majority of cases. Moreover, some of the patients had multiple problems along with hypertension and diabetes mellitus. Some of the other comorbidities were chronic kidney disease, dyslipidemia, atrial fibrillation, and lower respiratory tract infection. A small group of 25 patients did not suffer with any other major comorbidities.

Patients who received morning dose of the drug showed better and higher plasma concentrations in comparison with evening dose. The clinical reduction of BP was comparable in both groups but was slightly better in the morning group that evening group. The mean plasma levels in the morning group were 11.3 µg/ml (peak) and 5.2 µg/ml (trough) and in the evening group were 8.4 µg/ml (peak) and 2.8 µg/ml (trough).

PK and PD correlation was carried out for the given set of patients. Systolic and diastolic BP values were considered for PD parameter, and plasma concentration values were taken as PK parameter. Correlation coefficient "R^2" was calculated using the

formula $y = mx + c$. Systolic and diastolic values of both morning and evening dosing were individually calculated. For systolic BP of morning administration, R^2 for peak concentration was found to be 0.913 and R^2 for trough concentration was found to be 0.903 which clearly indicated the significant correlation between both parameters. These are depicted in Table 1.

Similarly, R^2 value for diastolic BP of morning administration was found to be 0.873 for peak concentration and 0.969 for trough concentration. Systolic BP of evening exhibited R^2 value of 0.986 and 0.955 for peak and trough concentrations, respectively. Diastolic BP of evening showed R^2 value of 0.931 and 0.896 for peak and trough concentrations, respectively. These findings clearly suggest that the PK parameters and the PD parameters are at par with each other in all the patients. Following Tables 2-4 represents the same.

Detailed statistical analysis was performed for the data set to ascertain mathematically the values and

Table 1: Correlation of systolic blood pressure (morning) and plasma levels

Morning systolic BP	Peak	Trough
110-119	13	5.5
120-129	12.4	5.2
130-139	12.1	4.9
140-149	10.26	3.4
150-159	8.6	2.2

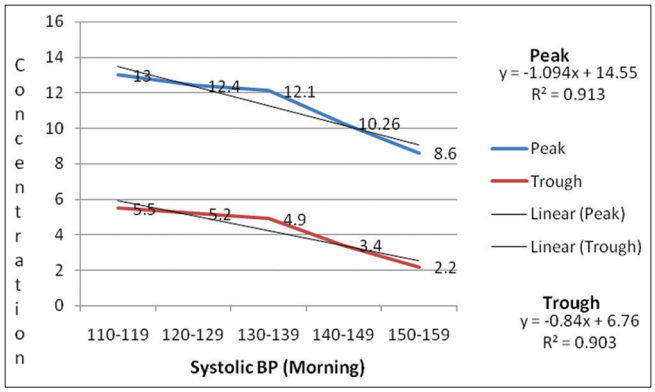


Table 2: Correlation of diastolic blood pressure (morning) and plasma levels

Morning diastolic BP	Peak	Trough
80-84	12.4	5
85-89	12	4.7
90-94	11.9	3.4
95-99	9.9	3
100-104	9.8	2.1
105-109	9.6	1.8

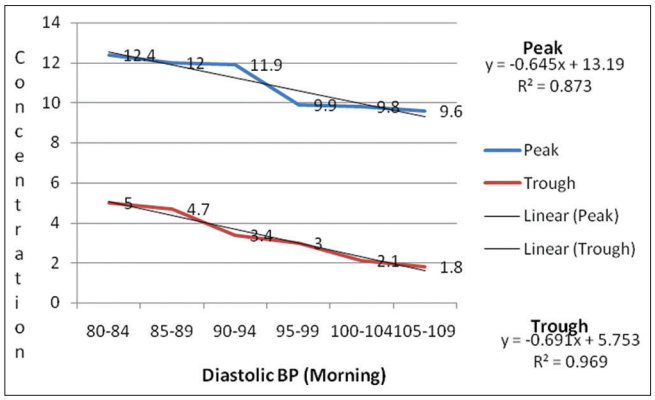


Table 3: Correlation of systolic blood pressure (evening) and plasma levels

Evening systolic BP	Peak	Trough
120-129	8.3	3.2
130-139	8.1	3
140-149	8	2.4
150-159	7.8	1.9
160-169	7.7	1.8

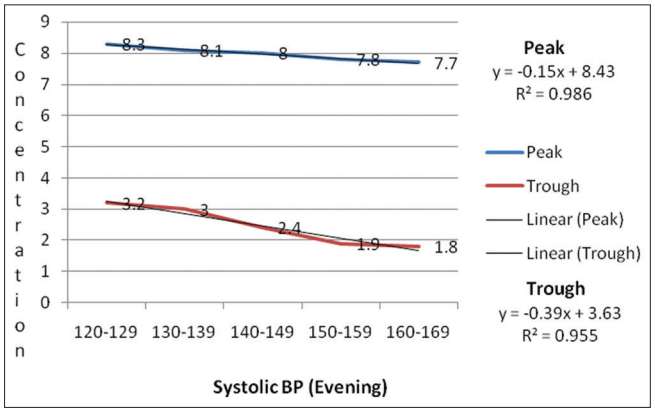
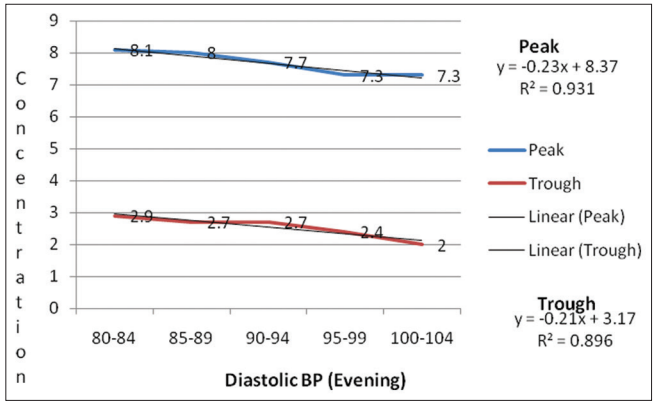


Table 4: Correlation of diastolic blood pressure (evening) and plasma levels

Evening diastolic BP	Peak	Trough
80-84	8.1	2.9
85-89	8	2.7
90-94	7.7	2.7
95-99	7.3	2.4
100-104	7.3	2



responses obtained. At the outset, the patient group was matched for age and gender and found that there was no significant difference in the demographics of both the groups and any change in the plasma concentration of the drug is not due to the demographical variations.

The correlation between the PK and PD parameters was analyzed statistically using Pearson's correlation test, and it was observed that there is a significant difference ($P < 0.001$) between the plasma concentrations and BP measurements (both systolic and diastolic) in both the time groups as illustrated in Table 5.

CONCLUSION

In accordance with the above-mentioned findings, it can be stated that the morning administration of metoprolol has better plasma levels throughout. The PK and PD parameters are at par with each other; there was a significant correlation between the BP and plasma concentrations in both the groups. Metoprolol administered in the morning can control the surge of BP and sympathetic tone thereby lowering the chances of morbidity and mortality in hypertensive patients. This can be considered as the preliminary finding to ascertain the various PK parameters to optimize the dosing schedule for hypertensive patients.

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Nil.

Conflicts of interest
There are no conflicts of interest.

Table 5: Statistical analysis of correlation between plasma concentrations and blood pressure

Time of administration	Correlations			
	Peak concentration (μg/ml)	Trough concentration (μg/ml)	Systolic	Diastolic
Morning				
Peak concentration (μg/ml)				
Pearson correlation	1	0.854**	−0.641**	−0.506**
Significant (two-tailed)		0	0	0
n	58	58	58	58
Trough concentration (μg/ml)				
Pearson correlation	0.854**	1	−0.637**	−0.529**
Significant (two-tailed)	0		0	0
n	58	58	58	58
Systolic				
Pearson correlation	−0.641**	−0.637**	1	0.811**
Significant (two-tailed)	0	0		0
n	58	58	58	58
Diastolic				
Pearson correlation	−0.506**	−0.529**	0.811**	1
Significant (two-tailed)	0	0	0	
n	58	58	58	58
Evening				
Peak concentration (μg/ml)				
Pearson correlation	1	0.635**	−0.048	0.135
Significant (two-tailed)		0.000	0.748	0.359
n	48	48	48	48
Trough concentration (μg/ml)				
Pearson correlation	0.635**	1	−0.329*	−0.121
Significant (two-tailed)	0		0.022	0.414
n	48	48	48	48
Systolic				
Pearson correlation	−0.048	−0.329*	1	0.713**
Significant (two-tailed)	0.748	0.022		0
n	48	48	48	48
Diastolic				
Pearson correlation	0.135	−0.121	0.713**	1
Significant (two-tailed)	0.359	0.414	0.000	
n	48	48	48	48

*Correlation is significant at the 0.05 level (two-tailed), **Correlation is significant at the 0.01 level (two-tailed)

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