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Variability of plasma concentrations of Amitriptyline and its metabolite Nortriptyline by Blood Pressure Alterations in Patients of Depression: A PK/PD Model

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Abstract

Co-morbid conditions need concomitant therapies. Treatment for depression is very difficult to be ascertained with a single pharmacotherapy but it needs polypharmacy. With the co-morbid conditions, like depression & hypertension, rheumatic arthritis and CVD needs pharmacotherapy acting on different receptors and the plasma concentration in systemic compartment is either enhanced or inhibited in these conditions.

Physiology of vascular system in designing dosage regimen in clinical practice is a complex phenomenon. To generate evidence in support of this probability, a single 100 mg dose of Amitriptyline an object drug was administered with 10 mg of Amlodipine as a precipitating drug in an open label, randomized parallel group, controlled clinical study based on PK/PD analysis model. Hypertensive patients with depression, test group (T_I), Hypertensive patients without depression, test group (T_{II}), Normotensive patients with depression, control group (C_I) and Normal healthy volunteers, control group (C_{II}), having 25 participants each were enrolled in this study. Plasma samples after single dose Amitriptyline at 0, 1, 2, 4, 8, 12, 24 hours were drawn along with measurement of heart rate, respiratory rate and blood pressure. A wash out period of 7 days for the two test groups (T_I and T_{II}) was given. Amlodipine 10 mg was administered which lowered the DBP by nearly 5 to 10 mm Hg, when the Amitriptyline was administered orally and the plasma samples were drawn for the analysis of Amitriptyline & its mtetabolite Nortriptyline along with PD parameters in a designed time event profile.

Plasma concentration of Amitriptyline and its metabolite Nortriptyline were extrapolated using a non-Compartmental model after Amlodipine induced fall in Diastolic blood pressure. C_{max} , T_{max} & AUC of Amitriptyline and Nortriptyline in both test groups (T_I and T_{II}) significantly increased.

Keywords: Amitriptyline, Nortriptyline, Amlodipine, Cmax, Tmax & AUC

Introduction

In-vitro and in-vivo studies show that magnitude of response to a drug is a function of its concentration in the fluid bathing the site(s) of action and hence therapeutic objective can be achieved by maintaining an adequate concentration of drug at that particular site for the stipulated duration of therapy. Adjustments are therefore needed, especially for drugs having narrow therapeutic window, steep concentration-response curve and are used for extended periods of treatments [1]. Therefore, for optimal drug administration and monitoring of treatments, knowledge is needed not only of kinetics of drugs but also how kinetics is influenced by resultant change in physiological processes by these drugs. Since blood flow may influence drug absorption, distribution and elimination, it is not surprising that pharmacokinetics of drugs may be altered in circulatory disorders [2].

Change in one physiological parameter causes change in others, hence drugs remain in dynamic state within biological system and events often happen simultaneously. Pathological conditions make the balance more complex [3]. Application of PK/PD model makes it possible to understand the quantitative relationships and describes how drugs work by relatively simple concept that can be used to optimize the best outcome of drug therapy [4]. PK/PD is based on the concept of target and its immediate relation to an effect. Biomarker assays help in identifying biological response to a drug candidate [5]. In this study for evaluation of plasma concentration alteration of the Amitriptyline as probe, the antihypertensive effect of dihydropyridine (Amlodipine) was taken as the biomarker for quantification of altered vascular physiology. Under routine dosing conditions patients develop inconsistent plasma concentrations, some develop inappropriately high plasma concentrations and experience additional adverse effects of the medication or some may lose the effect [6].There is a need to identify patients with co-existing hypertension and depression [7]. In elderly, mortality related to hypertension indirectly increases with depression [8]. If depression increases, hypertension also increases making the vascular cause of death very obvious [9]. Depression is to be checked primarily when there is co- morbidity like hypertension in a patient [10]. Amlodipine was effective in lowering blood pressure in mild to moderate hypertension and exerted favourable effects on renal haemodynamics and function [11]. The risk of harmful DDIs can be reduced by recognising variables that effect dose, concentration and effect relationships [12].

Aims & Objectives

Using PK/PD statistical model, study the risk of physiological interaction between object drug (Amitriptyline) and precipitating drug (Amlodipine) due to change in vascular physiology: Assessment of PD based PK alterations.

Material Methods

Subjects included in the study were Major Depressive Disorders (MDD), and subjects of hypertension. Depressive episodes were screened according DSM – IV classification [14]. Hypertensive subjects were screened using (JNC_7) classification of Blood pressure in adults based on average of properly measured readings at two or more period checks [14]. Patients of hypertension (SBP 120 to 140 mm Hg. DBP 80 to 95 mm Hg) were included in the study. Indirect measurement of Blood Pressure was done sphygmomanometer AHA [15].

ECG, Hb, Electrolytes, LFT, KFT and TFT were performed before administration of the subjects. Test result within normal range being mandatory requirement for inclusion criteria.

Research protocol was approved by the ethical committee constituted by SKIMS, a tertiary hospital. Written informal consent was obtained on the consent form in present of first family relation available.

It was a single dose, open label, randomized, parallel group controlled clinical study based on

PK/PD analysis model conducted over a period of two years during the year 2009 and 2010.

Participants (Male: Female, 12:13 or 13:12) in the age range of 20 to 55 years, who had hypertension and depression separately or as co-morbid conditions were included in the study. Normal healthy volunteers were also included as a control group. 25 participants selected after statistical randomization by Latin Square design were allocated to each of the following groups:

·Hypertensive patients with depressions; designated as Group $T_{I.}$

·Hypertensive patients without depression Group $T_{II.}$

·Normotensive patients with depression; Control Group $C_{I.}$

·Normal healthy volunteers; Control Group $C_{II.}$

Test group T_{Ia} and T_{IIa} along with the control groups C_I and C_{II} received single dose 100mg Amitriptyline (Triptomer Wockhard, Merind) orally. Serial blood sampling for PK at 0, 1, 2, 4, 8, 12 and 24 hr were drawn along with the monitoring of B.P, heart rate and respiratory rate. T_Ia and T_{II}a were re-designated as T_Ib and T_{II}b after 7 days washout period and re-admitted. Amlodipine 10 mg (Amlodac, zydus Medica) was administered to these test groups. After 4-5 hours when the DBP dropped down by approximately 5 - 10 mm Hg, Amitriptyline 100 mgs PO was administered and serial blood sampling for PK at 0, 1, 2, 4, 8, 12 and 24 hrs were collected in EDTA vials along with PD measurements. Only 2ml of blood each time was collected.

For PK/PD measurements, subjects were admitted in psychiatry ward for short hospital stay for 40 hours. First 12 hours were meant for stabilization and acclimatization to the hospital conditions. Blood samples were separated in separately labelled tubes and plasma samples obtained thereof were stored in – 70°c in deep freezer.

Estimation of Amitriptyline and its metabolite were performed by HPLC system, Thermofinnigan. The system works on Chromoquest software.

The method was validated at IIIM, Jammu (India) in collaboration with Pharmacological Division and Instrumentation Division.

The following optimized conditions [16, 17] on HPLC were used:

Mobile phase:	Acetonitrile(50%) & Phosphate buffer 50%
Flow rate:	1 ml/min
Column temp.:	40°C
Retention time:	Nortriptyline – 7.9' min Amitriptyline – 9.9 min
Detection :	239nm
Column:	C_8 (Varian), 250 x 4.6 mm; 5 micron
Atmospheric:	pressure 120 kg/cm^2
Conditions:	Reverse phase

Calibration curves of both Amitriptyline and Nortriptyline ranged from 5-100ng/ml. The assay had LLOQ of 5ng/ml for Amitriptyline as well as Nortriptyline. Lowest Limit of Detection (LLOD) for Amitriptyline was 2.5 ng/ml and that of Nortriptyline 3.5 ng/ml. Correlation Co-efficient of the linear calibration cure from 5 to 100 ng/ml of Amitriptyline is 0.992 and that of Nortriptyline is 0.998.

The extraction recoveries were consistent for both Amitriptyline and Nortriptyline between 90 to 95% at 5 ng/ml, 50 ng/ml and 100 ng/ml in these two co-mixtures. Intra-day and Inter-day reproducibility of Amitriptyline and Nortriptyline was within 10% co-efficient of variation at 5, 10, 20, 40, 80 and 100 ng/ml concentrations.

PK parameters were calculated non-compartmentally using Topfit Version 1.1 with two stage approach. Characteristics of the studied subjects were compared using student's t test (paired and unpaired), analysis of variance (ANOVA), Mann Whitney U test, chi square (x^2) test and spare Mans correlation analysis. The software used was MS-Excel, SPSS version 11.5 and Minitab 15.0 for calculating probability.

RESULTS

Anthropometric features revealed that there was no statistical difference in the mean age of males (40.0 ± 9.3 years) and females (41.6 ± 8.8 years) across the groups. The mean weight of males was 63.4 ± 7.5 kgs. and of females it was 58.7 ± 7.1 kgs. The mean weight in kgs of participants in T_I (63.5 ± 6.5), T_{II} (65.1 ± 4.6), C_1 (55.8 ± 6.7) and C_{II} (59.9 ± 8.8). The mean height of males was 166.9 ± 4.6 cms. and of females it was 158.7 ± 4.2 cms. The mean BMI of males was 22.7 ± 2.3 kgs/m^2 and of females it was 23.3 ± 2.8 kgs/m^2. BMI of the studied population cohorts of four groups was between 21.0 ± 2.6 and 24.2 ± 1.7 kgs/m^2. BMI was within normal range of 18.5 to 24.9 kgs/m^2 [18, 19].

For elucidation of evidence in support of eligibility for participation in the study, baseline investigations comprising of serum chemistry and thyroid function in addition to haemoglobin values investigated revealed that the profile was within the normal ranges of physiological function.

Results revealed that 12 hours after short hospital admission, when the participants had acclimatised to ward conditions, basal heart rate recorded without any significant difference across the test (T_I, T_{II}) and control (C_I, C_{II}) groups irrespective of depression and/or hypertension. 100 mg of Amitriptyline Po resulted in significant increase in heart rate from basal 73.0 ± 1.1 to 91.8 ± 2.4 per minute ($p<0.001$) in T_{Ia} and from 72.3 ± 0.7 to 91.6 ± 3.1 per minute ($p<0.001$) in T_{IIa} at 1 hour after administration. There was no significant change in the heart rate in the normotensive C_I and C_{II} groups. The relative tachycardia that developed in these groups had reverted back to the pre-treatment levels after first hour when recorded at second hour and the rate remained approximately around the pre-treatment values up to 24 hours of observation and investigation. The subsequent study on the same groups after a wash out period of 7 days and 10mg Amlodipine pre-treatment resulted in heart rate per minute of 72.5 ± 0.9 in T_{Ib} and 72.6 ± 2.0 in T_{IIb} recorded just before 100mg Amitriptyline administration. One hour after, heart rate for T_{Ib} was 72.8 ± 0.8 and for T_{IIb} it was 73.0 ± 2.0 showing no significant change in heart rate recorded for 24 hours at specific time intervals. Heart rate over the studied period otherwise remained stable. There was no significant variation in respiratory rate observed during 24 hour period after oral Amitriptyline

Analysis of Systolic Blood Pressure (systolic BP) changes in relation to time after 100 mgs of Amitriptyline orally showed a significant ($p<0.001$) decline within first hour in T_{Ia} from 134.0 ± 5.6 to 129.8 ± 5.7, T_{Ib} from 128.0 ± 3.3 to 125.9 ± 5.0, T_{IIa} from 134.4 ± 6.0 to 129.8 ± 5.3, C_I from 116.6 ± 6.5 to 112.0 ± 5.8 and C_{II} from 119.2 ± 2.8 to 115.6 ± 5.1 mm Hg). Thereafter decrease in systolic BP that was observed upto 8 or 12 hours in different groups, remained sustained without fluctuations. Remaining below the baseline, (pre-Amitriptyline treatment values), a gradual rise in systolic BP was discernable at 24 hours. The changes of systolic B.P in Amitriptyline treated T_{Ib} patients who had received prior Amlodipine, showed a slight decrease in systolic BP over 24 hours.

Analysis of diastolic blood pressure (Table1) showed that baseline values recorded just at Amitriptyline administration in pre-hypertensive groups T_{Ia} and T_{1Ia} expressed as 0 hour reading, were identical as 92.8 ± 2.5 mm Hg and remained between 92.6 ± 3.8 at 1 hour and 91.8 ± 2.4 at 24 hour ($p>0.05$) in T_{Ia} and between 90.0 ± 3.8 at 1 hour and 91.6 ± 3.1 at 24 hour in T_{IIa} without any significant change. In control groups, Amitriptyline did not affect 0 hour diastolic BP of C_I (74.8 ± 5.1) and C_{II} (76.0 ± 5.0). At 1 hour diastolic BP of C_I was 74.8 ± 5.1 and C_{II}

was 74.0 ± 5.0 mm Hg without significant change even at 24 hour remaining at 74.4 ± 5.1 for C_I and 78.0 ± 4.1 mm Hg for C_{II}. Amlodipine single dose in hypertensive patients with or without depression (T_{Ib} or T_{IIb}) resulted in acute drop in diastolic BP by approximately 10 mm Hg as against 5 mm Hg in systolic BP that persisted in a time event relationship across 24 hours. Amitriptyline administration after Amlodipine-induced fall in diastolic BP (T_{Ib} and T_{IIb}) demonstrated no significant alteration from 80.0 ± 0 at 0 hour to 82.0 ± 4.3 mm Hg at 1 hour varying insignificantly upto 81.6 ± 2.4 mm Hg at 24 hour (T_{Ib}) and from 81.3 ± 3.8 at 0 hour to 83.8 ± 4.3 mm Hg at 1 hour falling to 81.7 ± 3.9 mm Hg at 24 hour in T_{IIb} ($p>0.05$). No significant variability of diastolic BP in control groups across 24 hours was statistically identified.

Time (hr)	T_{Ia}	T_{Ib}	T_{IIa}	T_{IIb}	C_I	C_{II}
0	92.8 ± 2.5	80.0 ± 0.0	92.8 ± 2.5	81.3 ± 3.8	74.8 ± 5.1	76.0 ± 5.0
1	92.6 ± 3.8	82.0 ± 4.3	90.0 ± 3.8	83.8 ± 4.3	74.8 ± 5.1	74.0 ± 5.0
2	91.9 ± 3.7	80.9 ± 2.0	91.8 ± 2.8	81.7 ± 3.9	74.2 ± 4.9	75.2 ± 5.1
4	91.5 ± 3.6	81.8 ± 2.5	92.0 ± 2.5	82.0 ± 3.9	73.0 ± 5.4	74.8 ± 5.1
8	92.2 ± 2.5	81.4 ± 2.8	91.8 ± 2.8	82.2 ± 4.5	73.0 ± 5.0	76.0 ± 5.0
12	92.4 ± 2.9	81.8 ± 2.9	91.2 ± 3.0	83.0 ± 5.2	73.8 ± 4.8	75.2 ± 5.1
24	91.8 ± 2.4	81.6 ± 2.4	91.6 ± 3.1	81.7 ± 3.9	74.4 ± 5.1	78.0 ± 4.1*
Mean ± SD	92.2 ± 3.1	81.4 ± 2.7*	91.6 ± 3.0	82.2 ± 4.2*	74.0 ± 5.0	75.6 ± 5.0

Table 1: Effect of Amitriptyline given alone and after Amlodipine on diastolic Blood Pressure (mmHg)

*p< 0.001

Time after Treatment Analyte (hr)		T_{Ia}	T_{Ib}	T_{IIa}	T_{IIb}	C_I	C_{II}
0	amit	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	nor	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1	amit	10.1 ± 2.7	10.0 ± 3.6	11.5 ± 5.0	11.1 ± 4.8	8.8 ± 3.4	10.8 ± 5.1
	nor	5.9 ± 0.8	5.4 ± 2.0	5.7 ± 0.7	4.0 ± 2.7	5.8 ± 0.9	5.9 ± 0.9
2	amit	19.4 ± 8.9	19.7 ± 8.0	22.4 10.6	20.5 ±10.6	17.5 ± 6.2	21.6 ±10.3
	nor	7.6 ± 1.6	8.3 ± 1.7	7.6 ± 1.8	7.8 ± 2.0	7.3 ± 1.5	7.5 ± 1.5
4	amit	30.1 14.3	32.3 ±15.3	29.0 ±12.4	29.3 12.1	28.7 ±12.1	28.5 ±12.0
	nor	9.4 ± 1.8	10.4 ± 1.9	8.9 ± 1.9	9.6 ± 2.0	8.6 ± 1.9	9.4 ± 2.3
8	amit	27.7 ±12.4	28.0 ±12.1	25.4 ±10.9	27.0 10.2	24.6 ±10.4	24.6 10.2
	nor	9.4 ± 1.5	10.3 ± 1.9	8.4 ± 1.7	9.2 ± 2.1	9.4 ± 2.0	8.7 ± 1.9
12	amit	21.7 ± 9.5	23.3 ±10.2	19.5 ± 8.6	21.8 ± 8.2	19.7 ± 8.4	20.3 ± 9.0
	nor	7.8 ± 1.3	8.4 ±1.5	7.3 ± 1.5	7.6 ± 2.2	8.0 ± 1.4	7.3 ± 1.4
24	amit	16.2 ± 8.3	18.8 ± 9.0	15.2 ± 6.6	17.1 ± 7.0	15.5 ± 7.0	16.4 ± 7.8
	nor	6.7 ± 1.1	7.0 ± 1.2	6.2 ± 1.1	6.0 ± 2.1	6.5 ± 1.7	6.2 ± 1.0

Table 2: Bio-variability of Amitriptyline (Cp_{amit} ng/ml) single dose and metaboliteNortriptyline (Cp_{nor} ng/ml) in relation to time

amit = Amitriptyline; nor = Nortriptyline

While drawing correlations of systolic component of blood pressure with plasma drug concentrations, Overall Cp_{amit} and Cp_{nor} (Table 2) showed insignificant increase after decreasing systolic BP with Amlodipine in time relationship.

With respect to Nortriptyline in C_I group, $Cp_{nor.}$ of 5.8 ± 0.9 ng/ml increased to 8.6 ± 1.9 ng/ml when systolic BP shifted without a significant change from 112.0 ± 5.8 to 112.8 ± 6.8 mm Hg from 1 to 4 hr. Peak Cp_{nor} of 9.4 ± 2.0 ng/ml was recorded at 8 hour when systolic BP recorded as 112.0 ± 6.5 mm Hg showed no statistical change.

Results indicate that Amitriptyline and its metabolite Nortriptyline do not affect any significant change in diastolic blood pressure by themselves but when significant decrease was induced with oral Amlodipine from basal ≈'98 92 mm Hg in diastolic BP in T_{Ia} more or less 10 mm Hg to ≈'98 80 mm Hg in T_{Ib} , Cp_{amit} and Cp_{nor} registered significant increase ($p<0.001$). Cp_{amit} increased from 10.0 ± 3.6 ng/ml at 1 hour to 32.3 ± 15.3 ng/ml at 4 hour peak, and then decreased to 18.8 ± 9.0 ng/ml at 24 hour Cp_{amit} was also higher at 8 and 12 hour than that before Amlodipine induced fall in diastolic BP. Cp_{nor} showed similar pattern showing peak of 10.4 ± 1.9 ng/ml at 4 hour and then fall to 7.0 ± 1.2 ng/ml at 24 hour. All mean values of Cp_{amit} at stipulated time points from 2 hour were higher after Amlodipine induced fall in diastolic BP than before Amlodipine. Hypertensive participants without depression T_{IIa} had diastolic BP varying between 90.0 ± 3.8 mm Hg and 92.8 ± 2.5 mm Hg ($p<0.05$) as recorded at set time points across 24 hours in presence of increasing $Cp_{amit.}$ from 11.5 ± 5.0 ng/ml at 1 hour to 29.1 ± 12.4 ng/ml at 4 hour ($p<0.001$) followed by decrease to 15.2 ± 6.6 ng/ml at 24 hour. After Amlodipine, T_{IIb} fall in diastolic BP ranged between 81.7 ± 3.9 and 83.8 ± 4.3 mm Hg. ($p>0.05$) Cp_{amit} increased from 11.1 ± 4.8 ng/ml at 1 hour to 29.3 ± 12.1 ng/ml at 4 hour followed by decrease to 17.1 ± 7.0 ng/ml at 24 hours ($p<0.001$) Diastolic BP remaining lower, Cp_{amit} was higher after Amlodipine at least during 24 hours of estimation. After attaining 4 hour peak, higher levels of Cp_{amit} and Cp_{nor} were uniformly recorded in all test groups. Normotensive groups C_I had diastolic BP ranging between 73.0 ± 5.0 and 74.8 ± 5.0 mm Hg and healthy volunteers C_{II} had diastolic BP between 74.0 ± 5.0 mm Hg and 78.8 ± 4.1 mm Hg. C_I and C_{II} groups had Cp_{amit} and Cp_{nor} values comparable to T_{Ia} and T_{IIa} (without Amlodipine) as recorded at different intervals.

Discussion

Circulatory models were introduced into pharmacokinetics more than 25 years ago [20, 21]. The relevance of circulatory models in whole body pharmacokinetics appears justified since the underlying transport and distribution processes of drugs between blood and other tissues are determined by several factors including blood flow [22]. While reasoning the rationale for using non-compartmental physiological models over conventional models is that these models lack physiological reality and distribution parameters cannot be interpreted in terms of trans-capillary transport and tissue binding kinetics [23]. With circulatory pharmacokinetic models, parameters estimated on the basis of plasma concentration-time data are readily applicable to clinical situations [24]. The concept of present study was based on this analogy and was conducted to predict the possible early changes in plasma concentration during redistribution and re-equilibration phase of a drug if BP was altered. Cyclic illnesses need more medications during the treatment for an adverse effect, augmentation of desired effect or acceleration of onset of effect of first drug

[25]. The significant decrease in MIC of antibiotics after intravenous norepinephrine infusion has been reported [26]. In the study in question the careful search of object drug and precipitating drug based on their properties of having long half-life [27, 28] wider tissue distribution [29,30]. The drug kinetics can become variable with age [31]. To eliminate the age related variation in the present study, mean adult age was comparable to the mean ages of test and control participants.

In the present study 100 mg of Amitriptyline administered orally, to hypertensive patients with depression (T_{1a}) or without depression (T_{IIa}), normotensive subjects with depression (C_I) and normal healthy volunteers (C_{II}) , resulted in acute decline in systolic BP ($p<0.001$) possibly because the post synaptic $á_1$-adrenergic receptors are partially blocked initially contributing to early hypotensive effect.[32] In case of depression, there was a significant fall in systolic BP in T_{Ia} and in T_{IIa} possibly due to inhibition of enhanced central sympathetic outflow in depression associated with hypertension [33]. With continued use of Tricyclics, post synaptic $á_1$-adrenergic mechanisms restore to provide usual critical functions [34]. There was no statistical difference in systolic BP in Amlodipine treated T_{1b} and T_{IIb} patient groups after Amitriptyline was given.

Amitriptyline did not produce any change in diastolic BP even in hypertensive groups T_{Ia} and T_{IIa} . This clearly suggests lack of Amitriptyline influence on peripheral resistance and consequent changes in organ blood flow. These findings rule out the possibility of changes in haemodynamics and any self-inflicted changes in its own kinetics on that account. Amilodipine 10 mg orally resulted in significant fall ($p<0.001$) of diastolic BP in T_{Ib} and in T_{IIb} groups. Drugs belonging to calcium channel blocker (CCB) group exert vasodilator action on hepatic circulation, [35] prevent accumulation of erythrocytes in hepatic sinuses [36] and protect endothelial cells from damage and necrosis [37]. Because of long $T_{1/2}$ of Amlodipine, there are minimal fluctuations in plasma concentration and hence it produces less tachycardia, [38] as also shown by the results of this study.

There was no correlation between systolic BP and the plasma concentration of TCAs studied in hypertensive patients having depression (T_I) systolic BP in presence of significant Cp_{amit} variation between 10.1 ± 2.7 and 30.1 ± 14.3 ng/ml and Cp_{nor} variation between 5.9 ± 0.8 and 9.4 ± 1.8 ng/ml. Similarly, in hypertensive patients having no depression (T_{II}) systolic BP in presence of significant Cp_{amit} variation between 11.5 ± 5.0 and 25.4 ± 10.9 ng/ml and Cp_{nor} variation between 5.7 ± 0.7 and 8.9 ± 1.9 ng/ml. Similarly control groups of depressive (C_I) and normal healthy volunteers (C_{II}) failed to show correlation between Cp of analyte and systolic BP. The data suggests that plasma concentrations-time relationships of the marker drug or its metabolite and the systolic BP are independent variables and do not influence each other significantly.

Since the drug disposition incorporating all components of pharmacokinetic handling of the drug by the body is primarily dependant on the organ blood flow determined by vascular resistance, [39] it was hypothesized and tested that diastolic BP could have positive correlation with the kinetics of drugs, taking Amitriptyline in question as a surrogate marker along with its metabolite Nortriptyline in a PBPK model. The decline in diastolic BP by ≈'9810 mm Hg caused by Amlodipine, leading to increased blood flow and surface area of diffusion membrane by vasodilatation, showed rise in plasma concentration of Amitriptyline and Nortriptyline in the corresponding time relationships across the

study groups. In hypertensive depressive patients, fall in mean diastolic BP resulted in shift of peak Cp_{amit} from 30.1 ± 14.3 ng/ml to 32.3 ± 15.3 ng/ml and peak Cp_{nor} from 9.4 ± 1.8 to 10.4 ± 1.9 ng/ml. In patients with hypertension without depression, fall of mean diastolic BP demonstrated rise in the peak Cp_{amit} from 29.1 ± 12.4 to 29.3 ± 12.1 and Cp_{nor} from 8.9 ± 1.9 to 9.6 ± 2.0 ng/ml. Control groups C_I and C_{II} having diastolic BP had respective peak Cp_{amit} of 28.7 ± 12.1 and 28.5 ± 12.0 ng/ml and Cp_{nor} of 9.4 ± 2.0 and 9.4 ± 2.3 ng/ml, which were comparable to other groups. Diastolic BP of the control and the Amlodipine treated hypertensive groups was statistically similar. The corresponding time related differences in the Amitriptyline and Nortriptyline levels were also insignificant.

Conclusion

Despite plenty of literature discussing the rationale for a wider use of knowledge of vascular physiology with regard to pharmacokinetics of drugs, the available research is very scanty and the awareness among physicians about possibility of this issue assuming clinical relevance hardly exists.

The importance and practical implications of the study are that in emergency medicine when there is a change in haemodynamics by vasoconstrictors or vasodilators, the plasma cncentratations of the other co-administered drugs having narrow safety can prove to be fatal if the patient is admitted in the emergency. Thus there is a need of vigilance in emergency medicine when polypharmacy is used as a tool in therapeutics.

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