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Research Article

Variability in Systemic Pharmacokinetics of Amitriptyline by Blood pressure Alterations in Patients of Depression: A PD Based PK Analysis Model

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ABSTRACT

Physiology of vascular system in designing therapeutics is yet in its infancy. Co–Morbid conditions like depression and hypertension are complex physiological and pathological situations where PBPK drug interactions are highly probable due to change in systemic blood pressure resulting in organ perfusion that is an important determinant of drug dispersion. 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 with out 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 PK analysis along with PD parameters in a designed time event profile. Estimation of Amitriptyline and its metabolite Nortriptyline was performed by HPLC. Pharmacokinetic parameters were calculated using a non-compartmental model. After Amlodipine induced fall in DBP in both test groups, $T_{1/2}$, C_{max}, T_{max}, CL_T, AUC of Amitriptyline and Nortriptyline changed in both the test groups (T_I and T_{II}).

Keywords: PBPK, PK/PD analysis model, Amitriptyline and Nortriptyline

INTRODUCTION

Vast amount of new information on physiology of vasculature has become available but the relevance for clinical practice has not yet been well defined in many instances. The physiology of vascular system is more complex than has been imagined [1]. *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[2]. Step-by-step *PK* of a drug unfolds after its oral administration and further complexities are brought in by administration of concomitant treatments that interfere with the *PK* of initial drug through physiological milieu of the body functions [3]. The kinetic consequences of altered blood flow are examined with the realization that in therapeutic scenario the effects of change in more than one physiological variable needs to be considered[4]. 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[5]. In the present research, concept of using a disease model of hypertension-depression

was based on having rational use of object drug *viz.* Amitriptyline for patients with otherwise optimal functional capacity of drug handling organs and systems involved in *PK* process of object drug while haemodynamics would be readjusting itself to the new physiological set points in those patients whose organ blood flow is subjected to change. Decrease in peripheral resistance by a dihydropyridine vasodilator (Amlodipine), leading to change in blood flow[6], could produce a window to understand if and how pharmacokinetics could change for Amitriptyline, used in this study as a marker for studying *PK* outcome. Secondly, if treatment for hypertension and co-morbid conditions that may be a cause or consequence of hypertension, would merit a consideration of a possible physiological drug – drug interaction even with the two drugs like Amitriptyline and Amlodipine that are otherwise unreported to have any interactions[7]. The rationale of selecting Amitriptyline for the study was based on the fact that its tissue and plasma *PK* has been studied thoroughly and its safety, tolerability and ADRs are well assessed as it has a long history in the clinical practice[8]. In this study for evaluation of *PK* alteration of the Amitriptyline as probe, the antihypertensive effect of dihydropyridine (Amlodipine) was taken as the biomarker for quantification of altered vascular physiology.

For non-volatile drugs, there have been very few instances in which kinetic models of a drug have been linked to cardiovascular pharmacodynamic models[9]. In case of non cardiovascular drugs this approach was developed with a view to link simple cardiovascular *PD* with *PK* model as it has the potential to provide evidence for rational basis of devising regimens and adjustments in drug treatments that allows insight into logistics of controlling any therapeutic failures or side effects due to deviated *PK* as a result of physiological interaction. This model may make it possible to predict systemic consequences of other treatments in patients when dihydropyridine type of antihypertensive drug is prescribed for hypertension arising during course of pre-existing disease being treated. This approach has the potential to provide insight into difficulties that possibly could arise in implementing available knowledge of *PK* for most drugs in therapeutics as blood flow distribution can alter the essential components of drug kinetics. Therefore, the kinetic model of the treatment of a particular disease requires the model to have the physiological basis so as to be able to account for the changes of blood flow on the disposition of the drugs. When devising model of cardiovascular system, what merits consideration is that a drug with multiple mechanisms of action may produce a broad clinical effect in a heterogeneous population over a relatively narrow concentration range. Hence, on the same principle Amitriptyline was selected as a surrogate marker in this study in a cardiovascular model to identify changes in its concentration and the concentration of its metabolite Nortriptyline. There is a complex *PD* profile of TCAs. They produce a number of undesired as well as desired effects and are categorized as narrow therapeutic index drugs[10]. The study was purposely carried out using a single optimal dose of a model substrate drug with a low therapeutic index so that any possible increase in its levels after a co-prescribed drug will not result in a serious untoward outcome. There is an inter-individual variability in *PK* and *PD* of TCAs in general even in physically healthy people[11].

Age, co-morbid medical illness and concomitant medications are certain characteristics for efficacy, tolerability and safety issues in TCAs prescription. These have major impact on the treatment versus risk profile and likelihood of a successful outcome and can guide the clinician through a matrix of patient variables along with *PK* and *PD* variables[12].

AIMS & OBJECTIVES:

1. To know if and how pharmacokinetics of Amitriptyline varies after blood pressure is decreased with Amlodipine.
2. 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.

MATERIALS AND METHODS:

Subjects included in the study were Major Depressive Disorders (MDD), and subjects of hypertension. Depressive episodes were screened according DSM – IV classification[13]. Hypertensive subjects were screened using (JNC7) 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.

Research protocol was approved by the ethical committee constituted by SKIMS, a tertiary hospital. Written informal consent was obtained from the subjects involved in the study.

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_{IIa} were re-designated as T_{Ib} and T_{IIb} 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 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 – 70^0c in deep freezer. Estimation of Amitriptyline and its metabolite Nortriptyline was done after 9 months of storage under stipulated storage conditions.

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 temperature	40^0C
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 to 100 ng/ml. Lo The assay had LLOQ of 5 ng/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 mg/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 Interday 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 yrs) and females (41.6 ± 8.8 years) across the groups. But the relative age of the groups i.e. 46.2 ± 5.9 years for T_I, 42.6 ± 6.8 for T_{II}, 38.0 ± 10.3 for C_1 and 36.5 ± 9.5 for group C_{II}. The mean weight of males was 63.4 ± 7.5 kgs. and of females it was 58.7 ± 7.1 kgs. The mean weight 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) in kgs were included in this study. The mean height of males was 166.9 ± 4.6 cms. and of females it was 158.7 ± 4.2 cms. Mean respective group-wise height for T_I was (162.6 ± 6.0 cm.), T_{II} (164.2 ± 6.0 cm.), C_1 (163.2 ± 6.4 cm.) and C_{II} (161.6 ± 5.7 cm). 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 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.

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. 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. No statistical difference was perceptible in mean systolic BP values of male and female participants. The influence of gender factor on variability of systolic BP before and at serial time intervals after Amitriptyline revealed no significant difference.

Analysis of diastolic blood pressure showed that baseline values recorded just at Amitriptyline administration in pre-hypertensive groups T_{Ia} and T_{11a} 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 up to 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.

As illustrated in box plot (Fig. 1a), depicting treatments with Amitriptyline alone or Amitriptyline after Amlodipine in various groups, there was a significant increase in T½ of Amitriptyline from 18.8 to 23.1 hour ($p<0.001$) when given after Amlodipine in hypertensive patients (T_{IIb}) as represented by median values of the groups. Spread of distribution in IQR (Inter Quartile Region) of box plot has been uniformly towards third quartile with 0.6 to 1.9 fold variation across the groups. In group T_{Ia} there was statistically insignificant fall in median value of T½ from 20.1 to 18.8 hours after Amlodipine with increase in variability in third quartile. T½ of C_I and C_{II} was identical as depicted by their median lines. Fig. 1b shows Nortriptyline T½ across various group treatments. T½ median value has increased in hypertensive groups after Amlodipine (T_{Ib} and T_{IIb}) significantly ($p<0.001$) from 29.8 hours (T_{1a}) to 33.5 hrs. (T_{1b}) and from 31.3 hours (T_{11a}) to 34.5 hours (T_{IIb}) without much

IQR variability. Nortriptyline T ½ in control C_I and C_{II} has shown comparable variation.

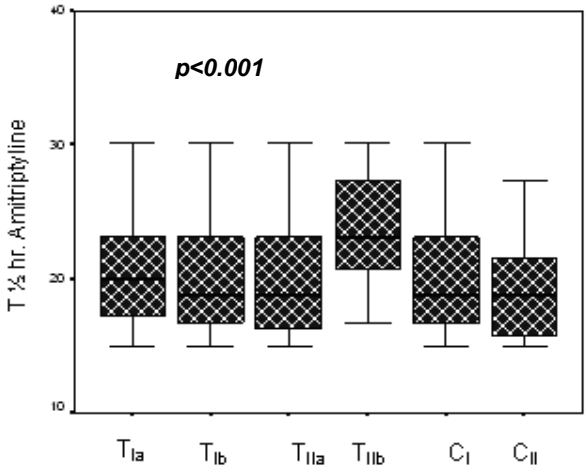

Fig 1a: Relationship between plasma T½ values of Amitriptyline in various treatment groups. Box plots depict first and third quartiles, and IQR (Inter Quartile Region) with median values indicated as Bold Median Line within the box. Thin lines mark the lowest and highest values.

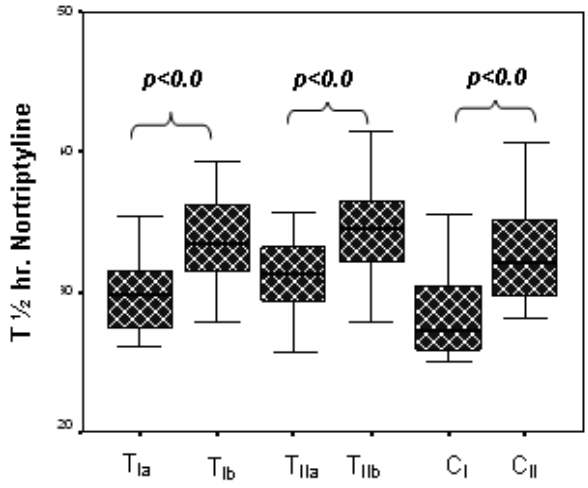

Fig 1b: Relationship of metabolite Nortriptyline T½ (hrs) to type of treatment (Amitriptyline or Amitriptyline after Amlodipine). The box plots show the Median line and 25-75% Inter Quartile Range (IQR) for half lives.

Box-plot of volume of distribution of (V_d) of Amitriptyline given alone (T_{1a}) and after Amlodipine (T_{1b}) in hypertensive patients with depression increased from 15.4 to 16.6 L/kg ($p<0.05$) as indicated by median line (Fig2). This change was associated with significant reduction in the variability of first quartile, thus narrowing down of IQR. In case of hypertensive patients without depression V_d of Amitriptyline increased significantly ($p<0.001$) from 15.0 L/kg (T_{11a}) to 18.2 L/kg (T_{11b}) after Amlodipine. Control groups had comparable median values of V_d (C_I = 16.4; C_{II} = 16.6 L/kg) through variability as IQR was more in C_I than C_{II}.

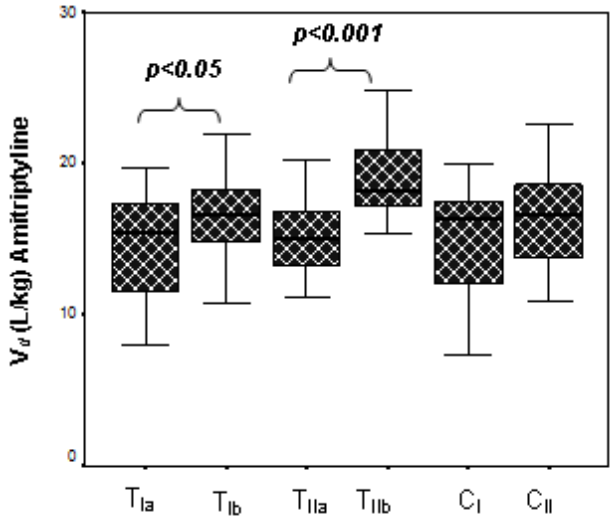

Fig 2: Box plot of V_d of Amitriptyline in various groups given alone or after Amlodipine indicating Median Value, IQR variability and extreme values. The median value of Total Clearance (CL_T) and variability of Inter Quartile Range (Fig. 3a) for Amitriptyline decreased when given after administration of Amlodipine in hypertensive groups from 8.6 in T_{Ia} to *7.7* ml.min^{-1}.kg^{-1} in T_{Ib} and from 8.7 in T_{IIa} to *7.7* ml.min^{-1}.kg^{-1} in T_{IIb}. The fall in the median CL_T was statistically significant ($p<0.001$. Total clearance of Amitriptyline in C_I and C_{II} did not show a significant difference ($p<0.05$).

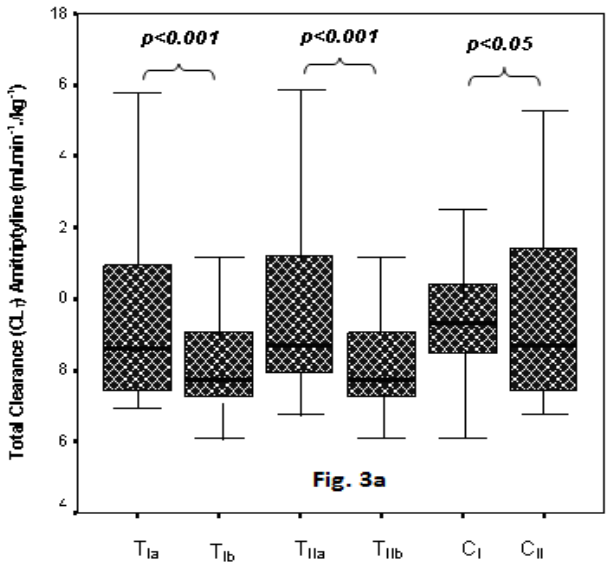

Fig 3a: Box plot representation of Total Clearance (CL_T) of Amitriptyline given alone and after Amlodipine in different groups

The metabolite Nortriptyline resulted in similar change of median values in T_{Ia} showing fall in CL_T from 7.6 to 7.1 ml.min^{-1}kg^{-1} (Fig 3b). Median value of CL_T in T_{II} did not show any difference between T_{IIa} and T_{IIb} (7.5 ml.min^{-1}kg^{-1}). Variability as indicated by IQR in T_I and T_{II} were significantly different. Control groups also depicted a significant difference ($p<0.001$) in CL_T median values as 7.1 and 8.3 ml.min^{-1}kg^{-1} for C_I and C_{II} respectively.

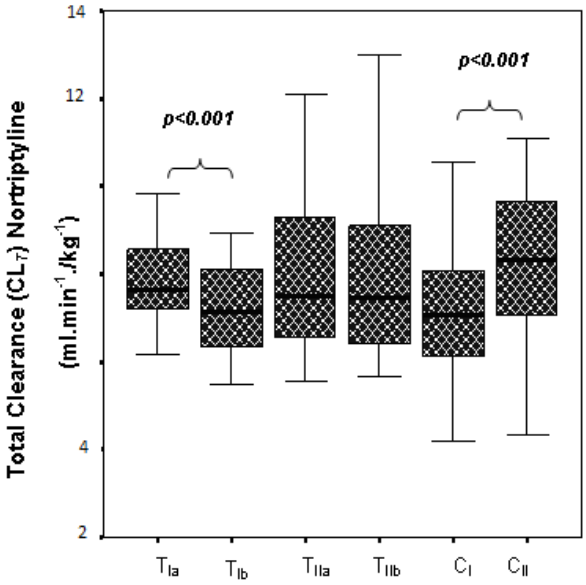

Fig. 3b: Box plot representing median values and degree of variability of Nortriptyline CL_T.

Figure (Fig 4a) illustrates that median value of $AUC_{(0-24)}$ of Amitriptyline has increased from 193.7 in T_{Ia} to 215.6 ng.ml^{-1}hr^{-1} in T_{Ib} ($p<0.001$) after reduction in diastolic BP by prior Amlodipine treatment. Similarly in T_{II} increase was evident from 191.8 in T_{IIa} to 204.3 ng.ml^{-1}hr^{-1} in T_{IIb} ($p<0.001$). The variability of the AUC as IQR, showed narrowing after Amlodipine. Alhough control groups C_I and C_{II} also showed some difference in median line of AUC, yet it was not significant ($p<0.05$).

$AUC_{(0-24)}$ of Nortriptyline also showed shift in both T_I and T_{II} groups towards Amlodipine treated subjects increasing from median value of 104.6 in T_{Ia} to 109.0 in T_{Ib} ($p<0.05$) and from 88.6 in T_{IIa} to 98.6 ng.ml^{-1}hr^{-1} in T_{IIb} ($p<0.001$) (Fig 4b). Nortriptyline AUC also demonstrated significant difference in control groups but paradoxically opposite to that of Amitriptyline. The median value of AUC of C_I was 122.6 as compared to 108.6 ng.ml^{-1}.hr^{-1} in C_{II}.

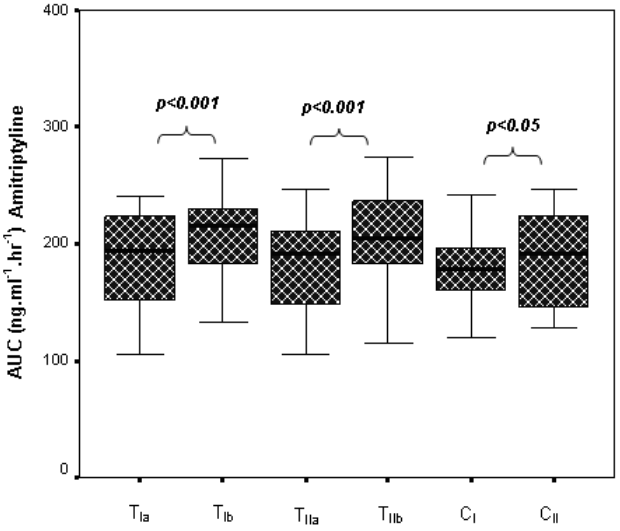

Fig. 4a: Box plot of Amitriptyline AUC $_{0-24}$ showing median values. IQR and variability in different groups.

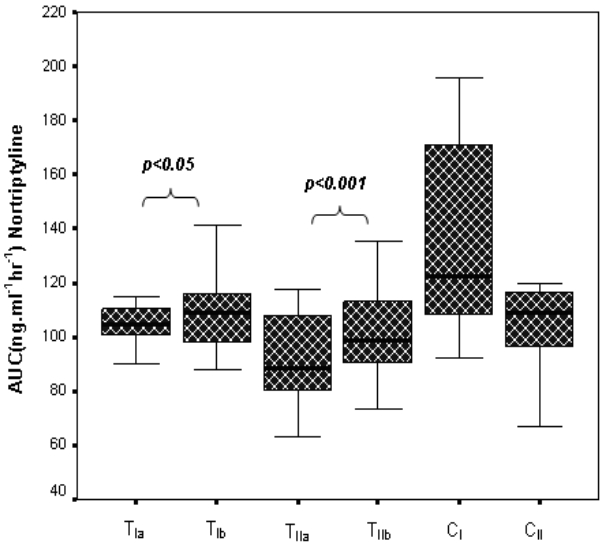

Fig 4b: Box plot of Nortriptyline AUC $_{(0-24)}$ hr.

Median value of Amitriptyline peak plasma concentration (C_{max}) as illustrated in Fig 5a, remained unchanged as 30.8 ng/ml in T_I after blood pressure alteration with Amlodipine. Also there was no statistical difference in C_{max} in T_{II} after Amlodipine. Control groups C_I and C_{II} though demonstrated some difference in median C_{max} it was not significant ($p=0.02$). C_{max} of Amitriptyline demonstrated significant variation in all groups as indicated by IQR.

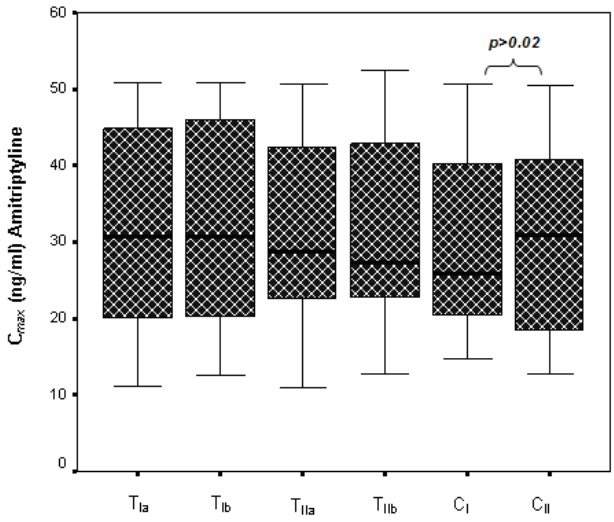

Fig 5a: Box plot of C_{max} of Amitriptyline: Group wise comparative Median value and variability before and after Amlodipine.

Nortriptyline C_{max} (Fig. 5b) demonstrated a significant increase in both hypertensive T_I and T_{II} groups. There was a significant increase ($p<0.001$) in Nortriptyline C_{max} from 10.7 (T_{Ia}) to 31.7 ng/ml (T_{Ib}) after Amlodipine. Similarly significant increase ($p<0.001$) was observed after Amlodipine in T_{IIa} from C_{max} of 9.7 to 27.4 ng/ml (T_{IIb}). The control C_I and C_{II} groups had identical median C_{max} values as 10.1 and 10.5 ng/ml respectively which were identical.

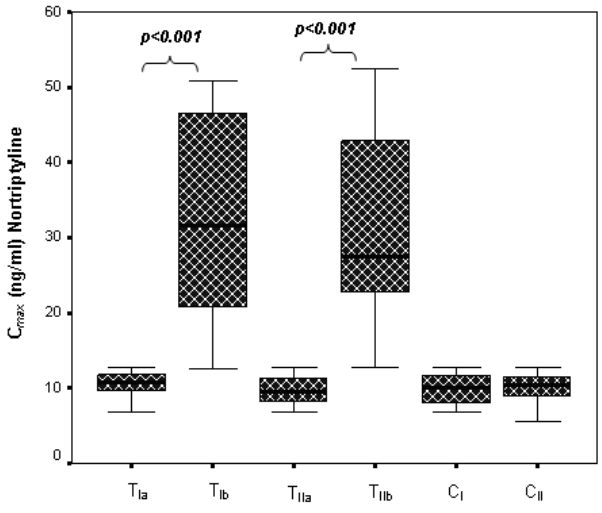

Fig 5b: Box plot of C_{max} Nortriptyline showing median values IQR variability

Analysis of median line of Time to maximum concentration (T_{max}) of Amitriptyline (Fig. 6a) revealed constant value of 4 hrs in all test and control groups. Amlodipine treatment did not influence median value of T_{max} in T_I or T_{II} groups. Group T_{IIa} showed high variability on both sides of median line that shifted to positive side of the median after Amlodipine (T_{IIb}).

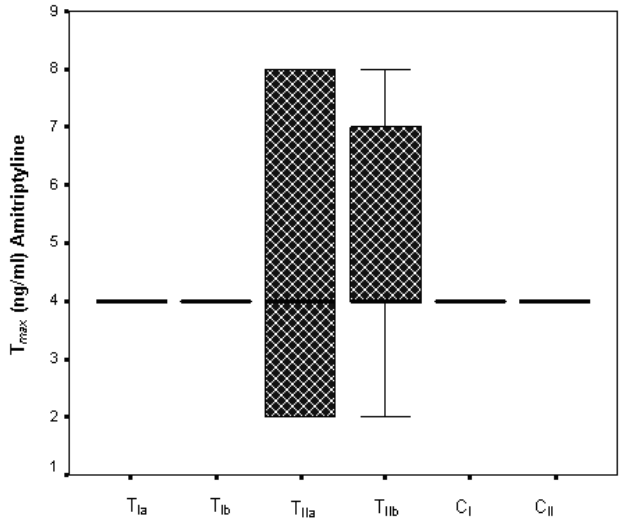

Fig 6a: Box plot representation of T_{max} of Amitriptyline with median line and IQR.

Median value of T_{max} of Nortriptyline (Fig. 6b) also remained constant at 4 hrs for all groups showing high variability on the positive side of Median line of each group. It was only for control group C_I that T_{max} was 8 hrs with variability on the negative side of Median line. There was a significant difference of T_{max} values in C_I and C_{II} ($p<0.001$).

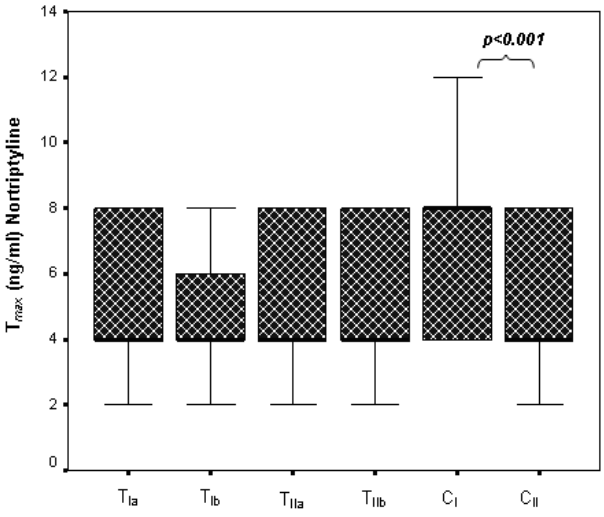

Fig 6b: Comparison of Nortriptyline (T_{max}) before and after Amlodipine

DISCUSSIONS

Although circulatory models were introduced into pharmacokinetics more than 25 years ago, [20, 21] less than 1%

used since then, analyzed clinical pharmacokinetic data that obey circulatory structure. 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]. The transport is believed as movement of drug across series of membranes, spaces and tissues, viewed as functional macroscopic membrane[23]. PBPK models have a rich information content than conventional pharmacokinetic models[24]. With circulatory pharmacokinetic models, parameters estimated on the basis of plasma concentration-time data are readily applicable to clinical situations[25].

The most common reason for MMU is treatment of patients who have more than one common chronic medical illness for example, hypertension, diabetes and depression[26]. Additional reasons for adding more medications include treatment of an adverse effect, augmentation of desired effect or acceleration of onset of effect of first drug [27].

Vasodilators like nitrates, nitroprusside etc. and co-administration of nitric oxide donors can cause potential catastrophic PBPK changes due to profound hypotension leading to significant change in pharmacodynamic response and therapeutic efficacy of a co-administered drug having high first pass metabolism especially for those drugs that have inherently variable kinetic profile. On the contrary, the response may be opposite if vasoconstrictors like epinephrine or norepinephrine are simultaneously administered as required in emergencies. The significant decrease in MIC of antibiotics after intravenous norepinephrine infusion has been reported [28].

In the study in question the careful search of object drug and precipitating drug based on their properties of having long half-life, [29, 30] wider tissue distribution [31, 32] and no direct drug-drug interaction between the two resulted in the selection of Amitriptyline as a probe for measuring pharmacokinetic changes of the drug that occur with alterations in blood pressure induced by Amlodipine. In addition, PDPK of Nortriptyline (metabolite of object drug) provided insight into the model through liver compartment so that the metabolism of Amitriptyline to Nortriptyline, becoming an input process would further help to understand the objectives.

Bioavailability factors of age, gender and BMI predominantly influence the response of treatments and pharmacokinetics [33]. Differences in response with age are likely to exist for certain drugs especially CNS active drugs that cannot be explained on the basis of differences in pharmacokinetics [34]. The drug kinetics can become variable with age [35]. Mean adult age for the population cohort studied, was comparable to the mean ages of test and control participants. Amlodipine, because of long $T_{1/2}$, there are minimal fluctuations in plasma concentration and hence it produces less tachycardia [36], as also shown by the results of this study.

As is clear, the maximum systemic exposure (C_{max}) of Amitriptyline has tendency to increase while time to this maximum exposure (T_{max}) tends to decrease. The changes were insignificant and highly variable and there is a significant increase in the metabolite Nortriptyline C_{max} after Amlodopine, may provide further evidence in support of the speculation that vasodilatation induced increase in blood flow including that of the liver may enhance the tissue exposure of drug as well as delivery to its metabolic target and exposure of the metabolic products.

Total systemic exposure of Amitriptyline and Nortriptyline for 24 hours (AUC_{0-24}) in hypertensive, depressive patients and normal volunteers did not show significant variation but after Amlodipine induced fall in blood pressure, the median value of AUC showed significant increase for Amitriptyline ($p<0.001$) and Nortriptyline ($p<0.05$). The results indicate that vasodilatation may have increased the absorption fraction of drug thus increasing the bioavailability of Amitriptyline and its metabolite Nortriptyline.

Box plot shows that after Amlodipine there was significant increase in the median value of Amitriptyline V_d in group T_I ($p<0.005$) and T_{II} ($p<0.001$) with decrease in its variability as compared to controls. The increase in V_d after fall in B.P clearly indicates that greater fraction of drug from plasma has moved to extra vascular tissue compartment.

The increase was also reflected in median values of T½ in box plot analysis (Fig. 5a) especially for Nortriptyline. Due to parallel changes in T½ of control groups the results were difficult to interpret. The half-life being controlled by and directly proportional to distribution and inversely to

clearance of drug; V_d of Amitriptyline also showed increase in hypertensive group after Amlodipine ($p<0.001$). This substantiates the evidence in favour of change in kinetic behaviour of the drug by alteration in blood pressure.

The variability also decreased after Amlodipine. CL_T of metabolite Nortriptyline decreased significantly ($p<0.001$) after Amlodipine possibly because CCBs do not produce any significant change in renal blood flow [37]. There was a significant variation between the control groups.

SUMMARY

This study was based on the hypothesis that the "*Pharmacokinetic Parameters*" of Amitriptyline undergo significant alterations after Amlodipine induced fall in blood pressure in patients of hypertension with or without having depression as a co-morbid disease. The study produced evidence in support of a significant *PK* to *PD* correlation. This data signifies the role of vascular physiology in therapeutics. Possibility of this PBPK interaction needs to be kept in view while treating hypertension which may be important for two reasons. Firstly the sizable populations suffering from primary or secondary hypertension and the co-morbidities requiring narrow therapeutic index drugs and secondly this may assume greater importance in critical intensive care where the disease management does not allow time for new steady state equilibrium for drug disposition kinetics.

REFERENCES

1. Danjan Strumper, Marcel E. Derieux et al. Physiology and pathophysiology of the peripheral circulation. Vascular Anethecia, Joel A. Kaplan, Carol L. Lake and Michael J. Murry. Edition IInd 2004, Page 1 - 13. Publisher Churchil Livingstone.
2. Malcolam Rowland and Thomas N. Tozer, "Clinical Pharmacokinetics Concepts and Applications" , Why Clinical Pharmacokinetics Edition 3rd 2007.
3. Javed Ali, et al, " A Text Book of Biopharmaceutics and Pharmacokinetics " 3rd Edition 2005 -2006.
4. Applied Biopharmaceutics and Pharmocokinetics; "Physiologic Drug Dristribution and Protein Binding" 5th Edition; Leon Shargel. MC Graw Hill : 251 – 254, 2005.
5. Egorin MJ. Overview of recent topics in clinical pharmacology. 42 suppl. S22 – S30, 1998.
6. Bott GR and Saxena PR. Vasodilators and regional blood flow. Indian J.Pharmac 1985, 21 – 29.
7. Joe R. Anderson and James J. Nawarsks. Cardio vascular drug-drug intercalations. Cardiology Clinics 2001; Volume 19, issue 2, 215 – 234.
8. Corrado Barbui, Mathew Hotopf. Amitriptyline Vs The rest : still leading antidepressant after 40 years of randomized controlled trails. The British Journal of Psychiatry 2001; 178 : 129 – 144
9. Michael J. Burke, Sheldon H. Preskorn Standard Antidepressent Pharmacotherapy for the acute treatment of mood disorders. Back to Psychopharmacology – The Fourth Generation Progress. Page 1 – 50.
10. Richard N Upton and Guy Ludbrook. Pharmacokinetic – Pharmacodynamic modelling of cardiovascular effects of drugs – method development and application to magnesium in sheep. BMC Pharmacology 2005, 5: 5; 1471 – 2210.
11. Shad MU, Preskorn SH. Antidepressants in Levy RH and others, Eds: Metabolic Drug Interactions. Philadelphia, 2000, Lippincort Williams and Wilkins, PP 563 – 577.
12. Preskorn S, Fast G. Therapeutic drug monitoring for antidepressants: efficacy, safety and cost effectiveness. J of Clin Psychiatry 1991;1 (52): 23 – 33.
13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edition (DSM-IV) Washington, DC; APA, 1994: 317 – 339.
14. Pickering, et al. JNC 7 Express. The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation and treatment of High Blood Pressure. Hypertension 2002; 40: 795 – 796.
15. Thomas G. Pickering, Lawrence J. Appel, Bonita E. Falter, Martha N. Hill, Daniel W.Jones. Recommendations of blood pressure measure-ment in humans. Hypertension 2005; 45: 142
16. Alferd M. Nyanda, Mathew G. Numes, et al. A simple high performance liquid chromatography method for the quantitation of tricyclic antidepressant drugs in human plasma or serum. Clinical Toxicology 2000; 38(6): 631 – 636.
17. Zarghi A, Dadashzadeh S, Kiayi Z. Determination of amtriptyline in plasma samples by performance liquid chromatography. Boll Chim Farm 2001 Nov – Dec; 140(6): 458 – 461.
18. Gorber CM, Tremblay D. Mother and Grorber B. A comparison of direct vs. Self report measure for crossing height, weight and body mass index: a systematic review, Obesity Reviews 2007; 8: 307 – 326.
19. Bruce Green and Stephen B. Duffull. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacology 2004 August; 58 (2): 119 – 133.

20. Sandy K Pang, Michael Weiss, et al. Advances pharmacokinetic models based on organ clearance, circulatory and practical concepts. The AAPS Journal 2007; 9(2): Article 30 (http://www.aa.psj.org).
21. Weiss M, Forester W. Pharmacokinetic model based on circulatory transport. Eur J Clin Pharmacol 1979; 16: 287 – 293.
22. Upton RN, Grant C, Martinez AM, et al. Recirculatory model of fentanyl disposition with the brain as the target organ. Br J Anesth 2004; 93: 687 – 697.
23. Nestorov I. Whole body physiologically based pharmacokinetic models. Expert Opinion Drug Metab Toxicology 2007; 3: 235 – 249.
24. Cutler DJ. A linear recirculation model for drug disposition. J Pharmacokinet Biopharm 1979; 7: 101 – 116.
25. Rescigno A, Beck JS. The use and abuse of models. J Pharmacokinet Biopharm 1987; 15: 327 – 344.
26. Charles B. Nemeroff, Sheldon H. Preskorn. Antidepressant drug: drug interaction; clinical relevance and risk management. CNS Spectr 2007; 12(5) suppl 7:1 – 16.
27. Brain B. Hoffman. Therapy of hypertension. Goodman and Gilman's The Pharmacological Basis of Therapeutic 11th Edition, 2006: 845 – 868.
28. Preskorn S, Lacey R. Polypharmacy: when is it rational? J Pract Psychiatr Behav Health 1995; 1: 92 – 98.
29. Abernethy DR. Pharmackokinetics and pharmacodynamics of amlodipine. Cardiology 1992; 80 (suppl 1): 31 – 36.
30. Breyer P, Paff U, Gaertner HJ, Kreuter F. Antidepressant effect and pharmackokinetics of amitriptyline with considerations of unbound drug and 10 – hydroxylnortriptyline plasma levels. Psychopharma-cology 1982; 76: 240 – 244.
31. Faulkner JK, McGibney D, Chasseand LF, Perrry JL, Taylor IW. The pharmackokinetics of amlodipine in healthy volunteers after single intravenous and oral doses and after 14 repeated oral doses given once daily. Br J Clin Pharmac 1986; 22: 21 – 25.
32. Borga O, Azarnoff DL, Plym Forshell G. Plasma protein binding of tricyclic antidepressants in man. Biochem Pharmacol 1969; 18: 2141 – 2142.
33. Yonkers KA, Kando JC, Cole JO. Gender differences in pharmacokinetics and pharmacodynamics in psychotropic medication. Am J Psychiatry 1992; 149: 587 – 595.
34. Mangoni AA and Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2004; 57 (1): 6 – 14.
35. Harman D. Aging: phenomena and theories. Ann NY Acad Sci 1998; 854 : 1 – 7.
36. Rudd P. Partial compliance: implications for clinical practice. J Cardiovasc Pharmacol 1993; 22 (suppl A): S1 – S5.
37. Harold D. Green, Robert N. Lewis, Neil D. Nickerson, Arnold L. Heller. Blood flow: peripheral resistance and vascular tonus, with observations on the relationship between blood flow and cutaneous temperature. Am J Physiol 1994; 141: 518 – 536.

