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Pharmacology

PHARMACOKINETIC INTERACTIONS BETWEEN CONCOMITANTLY ADMINISTERED CARBAMAZEPINE WITH RIVAROXABAN

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ABSTRACT The present study was aimed to evaluate any possible pharmacokinetic interactions between Carbamazepine and Rivaroxaban. Study was conducted in Male Wistar rats; the treatment was given on day one and day 8 both alone Carbamazepine and Rivaroxaban and concomitantly used both the drugs. The results were showed no significant difference in the t_{max} of Carbamazepine alone and combination with Rivaroxaban on day 1 and day 8 respectively. These was significant decrease in both c_{max} and t_{max} of Rivaroxaban alone and combination of Carbamazepine on day 1 and day 8 respectively. Carbamazepine combined-gp inducer and strong CYP3A4 inducer, therefore it may induce the metabolism of Rivaroxaban so it reduces the concentrations and increase the elimination rate. Based on the results obtained from kinetic study it was evident that the single dose of Carbamazepine and Rivaroxaban individually and concomitantly treated shows statistically significant interactions in its pharmacokinetic parameters.

KEYWORDS : .Carbamazepine, Rivaroxaban. Pharmacokinetic drug interactions, Wistar rats.

INTRODUCTION

Pharmacokinetic interactions can occur when one drug interferes with another one and alters the level of the drug or its metabolite or both of them (1, 2). This kind of interactions between AEDs most commonly occurs due to displacement of a drug from binding with plasma proteins or modification of hepatic metabolism. Interactions involving protein binding displacement are prominent only among the highly protein-bound AEDs (more than 90%), i.e. Phenytoin (PHT), Tiagabine (TGB) or Valproic acid (VPA) (1, 2, 3).

Guidelines recommend that patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) should receive anticoagulant treatment, starting with parenteral induction using an agent such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux (4, 5). The parenteral anticoagulant is then overlapped with an oral vitamin K antagonist (VKA; e.g. warfarin) until the latter has reached its target anticoagulation level, after which the parenteral agent is discontinued. VKA therapy is continued for as long as the risk of recurrent venous thromboembolism (VTE) outweighs the risk of bleeding (4, 5). This approach is effective if managed well but does present challenges, both in the acute phase of treatment, when two drugs must be administered together, and over the course of long-term therapy, because of the well-documented limitations of VKAs. The latter include a slow onset and offset of action, multiple drug and food interactions, and variable responses, which necessitate frequent coagulation monitoring and dose adjustments (6).

Fast-acting, single-target, direct oral anticoagulants with more predictable pharmacological properties than VKAs and fewer drug interactions, and that do not require routine coagulation monitoring, have been developed. Four of these anticoagulants (rivaroxaban, apixaban, edoxaban and dabigatran) have been tested against standard therapy in randomised, controlled clinical studies for the treatment of acute VTE and secondary prevention, either alone or after parenteral induction (4, 5, 6, 7, 8, 9, 10, 11). Rivaroxaban, a direct Factor Xa inhibitor, is approved in the European Union and the United States for the single-drug treatment of DVT and PE and the secondary prevention of recurrent VTE in adults. Apixaban, a direct Factor Xa inhibitor, and dabigatran, a direct thrombin inhibitor, are also approved for VTE treatment in the European Union, and dabigatran is also licensed in this indication in the United States.

The approved dose regimen for rivaroxaban in VTE treatment is 15 mg twice daily for the first 3 weeks, and 20mg once daily thereafter for the specified duration of therapy (12). This schedule was derived based on the fundamental pharmacological properties of rivaroxaban, data from phase II dose-finding studies, pharmacokinetic modelling (13) and randomised phase III clinical trials.

MATERIALS AND METHODS

Materials:

Drugs and chemicals

Carbamazepine and Rivaroxaban were procured from MSN laboratories, Hyderabad as a gift sample. HPLC grade solvents (methanol and water) were procured from finar chemicals Ltd., Ahmadabad. All other chemicals used were analytical grade.

Animal study

Male Wistar rats (weighing 200-220gms) were procured from the animal house CMR College of Pharmacy, Hyderabad. Animals were randomly divided into four groups each group contains six animals. Each rat was maintained under controlled lab environment atmosphere humidity of 50%, fed with standard pellet diet and water *ad libitum*. The protocol of animal study was approved by the institutional animal ethical committee with No. IAEC/1657/CMRCP/T2/Ph D-16/68.

Study Design

The rats were grouped as follows:

Group I:Carbamazepine alone in single dose / day in healthy rats.
Group II:Rivaroxaban alone in single dose / day in healthy rats.
Group III:Carbamazepine and Rivaroxaban concomitant administration in healthy rats as a single dose / day.

Collection of Blood Samples

After administration of the drugs, blood samples of 0.5 ml were drawn from each anesthetized (isoflurane) rat at pre-determined time intervals was collected from the retro-orbital plexus using a capillary tube into pre-labelled eppendorf tubes containing 10% of K_2EDTA anticoagulant (20µL). The time intervals for the sample collection were 0 (Pre dose), 0.5, 1, 2, 4, 6, 8 and 24 hrs (post dose), Equal amount of saline was administered to replace blood volume at every blood withdrawal time. Plasma was obtained by centrifuging blood samples by using cooling centrifuge (REMI ULTRA) at 3000 rpm for 5 minutes. The obtained plasma samples were transferred into pre-labelled micro centrifuge tubes and stored at −30°C until bio analysis of pharmacokinetic and pharmacodynamic parameters. As described above, all the procedures were followed on day 8 also. Pharmacokinetic parameters were calculated by non-compartmental analysis by using Win Nonlin® 5.1 software. Concentrations obtained from the above bio-analytical method were compiled.

Method of Analysis

Preparation of Plasma Samples for HPLC Analysis

Rat plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1min. After centrifugation (5000 – 6000 rpm for 10 min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 2001 of mobile phase was injected for HPLC analysis.

For HPLC an Inertsil ODS 3V, 250x4.6 mm, C18 column with 5µm particle size and the mobile phase consisting of acetonitrile and water (35:65, v/v), the flow rate was maintained at 1ml/min and the eluent was monitored at 220 nm. The calibration curves of peak area versus concentration, which was linear from 2-20µg/ml for Carbamazepine and 3.12-100µg/ml for Rivaroxaban respectively. The retention times of Carbamazepine and Rivaroxaban were found to be 4.7 and 6.6min respectively.

Standard calibration curve of Carbamazepine and Rivaroxaban in rat plasma

Different concentration (0.05, 0.1, 0.5, 1, 5, 10, 20, 40ng/ml) of Carbamazepine, Rivaroxaban in plasma were prepared for calibration curve. The samples were treated as above for protein precipitation method and peak areas of Carbamazepine and Rivaroxaban were noted down. The peak area ratios obtained at different concentrations of the Carbamazepine, Rivaroxaban were plotted using UV – Vis detector at 220 nm.

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24hrs, which was determined by linear trapezoidal rule and AUC_{0-} refers to the AUC from time at zero hours to infinity.

The AUC_{0-} was calculated using the formula $AUC_{0-t} + [C_{last}/K]$ where C_{last} is the concentration in g/ml at the last time point and K is the elimination rate constant.

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life [t½]. Volume of distribution (V/f) total clearance (Cl/f) and mean residence time for each subject using a non-compartmental analysis by using Win Nonlin® 5.1 software.

Statistical Analysis

Statistical comparisons for the pharmacokinetic – Pharmacodynamic study among, Carbamazepine, Rivaroxaban alone and in combination groups and plasma concentration – response study among concentrations and time were carried out with student's paired T-Test a value of $P<0.05$ was considered to be statistically significant. Data were reported as mean S.E.M linear regressions were used to determine the relationship between total plasma concentrations and pharmacokinetic and pharmacodynamic parameters. The mean concentration versus time profile of Carbamazepine and Rivaroxaban in rat plasma is shown in **Figures 1, 2, 3 and 4.**

RESULTS AND DISCUSSION

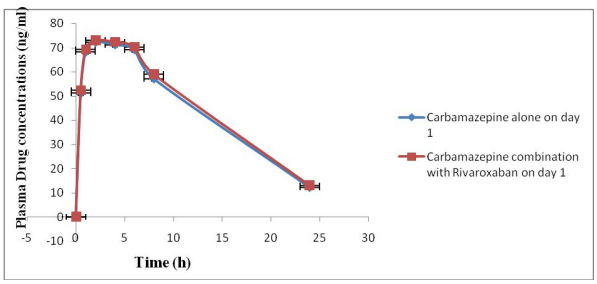

Figure 1: Mean ± S.E.M, plasma levels (ng/ml) of Carbamazepine alone and in Combination with Rivaroxaban on day 1

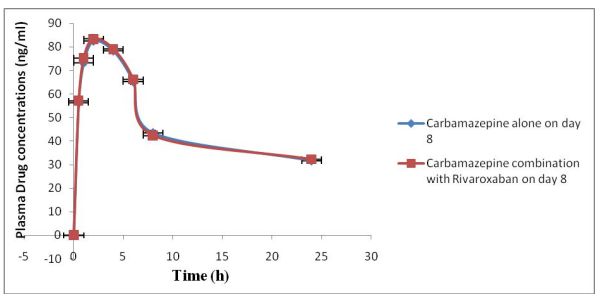

Figure 2: Mean ± S.E.M, plasma levels (ng/ml) of Carbamazepine alone and in Combination with Rivaroxaban on day 8

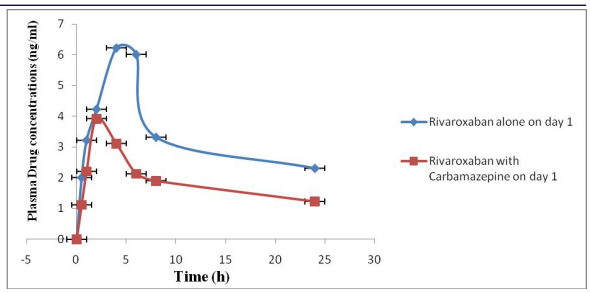

Figure 3: Mean ± S.E.M, plasma levels (ng/ml) of Rivaroxaban alone and in Combination with Carbamazepine on day 1

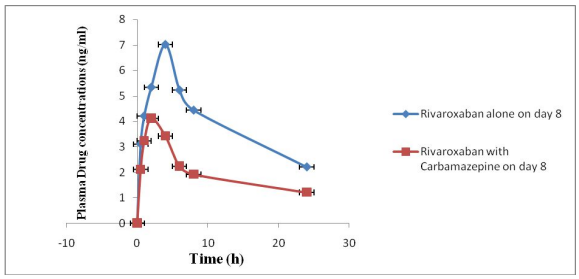

Figure 4: Mean ± S.E.M, plasma levels (ng/ml) of Rivaroxaban alone and in Combination with Carbamazepine on day 8

Table 1: Mean ± S.E.M, pharmacokinetic parameters of Carbamazepine alone and in Combination with Rivaroxaban on day 1

parameters	Carbamazepine alone	Carbamazepine combination with Rivaroxaban
C_{max}(ng/ml)	75.24±0.39	76.03±0.12
t_{max}(h)	3±0	3±0
AUC_{o-t}(ng/ml/h)	463.45±4.24	466.27±4.52
AUC_{o-inf}(ng/ml/h)	668.82±4.50	671.15±5.85
$T_{1/2}$(h)	6.56±0.28	6.64±0.09

Table 2: Mean ±S.E.M, pharmacokinetic parameters of Carbamazepine alone and in Combination with Rivaroxaban on day 8

parameters	Carbamazepine alone	Carbamazepine combination with Rivaroxaban
C_{max}(ng/ml)	87.52±3.22	88.41±3.12
t_{max}(h)	3±0	3±0
AUC_{o-t}(ng/ml/h)	577.36±5.38	581.18±6.49
AUC_{o-inf}(ng/ml/h)	683.36±7.63	689.49±7.74
$T_{1/2}$(h)	6.4±0.24	6.08±0.18

Table 3: Mean ± S.E.M, pharmacokinetic parameters of Rivaroxaban alone and combination with Carbamazepine day 1

parameters	Rivaroxaban alone	Rivaroxaban in combination with Carbamazepine
C_{max}(ng/ml)	6.02±1.03	3.92±1.03
t_{max}(h)	4±0	2±0
AUC_{o-t}(ng/ml/h)	64.39±1.20	35.9±0.118
AUC_{o-inf}(ng/ml/h)	65.23±1.36	37.49±0.808
$T_{1/2}$(h)	7.22±0.49	3.03±1.11

Table 4: Mean ± S.E.M, pharmacokinetic parameters of Rivaroxaban alone and combination with Carbamazepine day 8

parameters	Rivaroxaban alone	Rivaroxaban in combination with Carbamazepine
C_{max}(ng/ml)	7.02±1.03	4.12±1.03
t_{max}(h)	4±0	2±0
AUC_{o-t}(ng/ml/h)	84.39±1.20	42.9±1.18
AUC_{o-inf}(ng/ml/h)	85.23±1.36	47.49±1.88
$T_{1/2}$(h)	7.32±0.49	3.43±0.11

DISCUSSION

In the present study, Carbamazepine is completely absorbed after oral administration with peak plasma concentration of 75.24±0.39ng/ml after 3hrs of dosing on day 1. In combination with Carbamazepine and Rivaroxaban on day 1, the peak plasma concentration of Carbamazepine 76.03±0.12ng/ml occurred 3hr after dosing. There was no significant increase in peak plasma concentration levels. Similarly Rivaroxaban is completely absorbed after oral administration with peak plasma concentration 6.02±1.03g/ml occurred 4hr after dosing on day 1, in combination with Carbamazepine and Rivaroxaban on day 1. The peak plasma concentration of Rivaroxaban 4.12±1.03ng/ml occurred 2hr after dosing. There was significant decrease in the peak plasma concentration levels, on day 8 of Carbamazepine alone and with combination of Carbamazepine with Rivaroxaban on day 8. Peak plasma concentrations are 87.52±3.22ng/ml and 88.41±3.12ng/ml, Rivaroxaban on day 8 and combination with Carbamazepine concentrations are 7.02±1.03ng/ml and 4.12±1.03ng/ml respectively (results were showed in **Table 1, 2, 3, 4**). There was significant difference in peak plasma concentration on day 8 ($P>0.05$). There was a significant difference was observed in peak plasma concentration and $t_{maxa.}$ Rivaroxaban is a first available active direct factor Xa inhibitor which is taken by mouth. The maximum inhibition of factor Xa occurs four hours after a dose. The effects last approximately 8–12 hours, but factor Xa activity does not return to normal within 24 hours, so once-daily dosing is possible. Carbamazepine is a medication used primarily in the treatment of epilepsy and neuropathic pain. It is not effective for absence seizures or myoclonic seizures. It is used in schizophrenia along with other medications and as a second line agent in bipolar disorder. Carbamazepine combined-gp inducer and strong CYP3A4 inducer Therefore it may induce the metabolism of Rivaroxaban so it reduces the concentrations and increase the elimination rate.

CONCLUSION

In the present study, based on the results obtained from kinetic study it is evident that the single dose of Carbamazepine and Rivaroxaban individually and concomitantly treated shows statistically significant interactions in its pharmacokinetic parameters.

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