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International Journal of Pharmaceutical Sciences and Drug Research 2018; 10(5): 406-409

Research Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

Pharmacokinetic Interactions between Concomitantly Administered Phenytoin with Rivaroxaban

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ABSTRACT

In the present investigation it was aimed to evaluate any possible pharmacokinetic interactions between Phenytoin and Rivaroxaban. Study was conducted in Male Wistar rats; animals were divided into three groups. Group 1 received Phenytoin alone, Group 2 received Rivaroxaban alone and Group 3 received Phenytoin and Rivaroxaban concomitantly. The treatment was given for 8 days and the blood samples were collected on day 1 and day 8. The samples were analyzed by HPLC. The results were showed no significant difference in the Pharmacokinetic parameters of Phenytoin in presence of Rivaroxaban. Whereas Rivaroxaban showed significant decrease in both C_{max} and t_{max} in combination with Phenytoin. Phenytoin is a 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 pharmacokinetic study it was evident that the single dose of Rivaroxaban in combination with Phenytoin shows statistically significant interactions in its pharmacokinetic parameters.

Keywords: Phenytoin, Rivaroxaban, Anticoagulant, Pharmacokinetic interactions.

DOI: 10.25004/IJPSDR.2018.100507 **Int. J. Pharm. Sci. Drug Res. 2018; 10(5): 406-409**

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 29 July, 2018; **Revised:** 21 August, 2018; **Accepted**: 24 August, 2018; **Published:** 23 September, 2018

INTRODUCTION

A drug interaction occurs when the usual effects of a drug are enhanced or diminished by another drug being taken by the patient. In most cases, these interactions are unintentional and come to the attention of clinicians due to a therapeutic failure or adverse event that is undesirable. Poly pharmacy and drug interactions are common particularly among seniors. A survey of elderly individuals living in the community reported that 29% were taking five or more prescription drugs regularly. [1] Oral Anticoagulants (DOACs), such as the thrombin-inhibitor dabigatran and the Factor Xa-inhibitors Rivaroxaban, Apixaban, and edoxaban has provided a safe and effective alternative to vitamin-K antagonists (VKA) for the prevention of systemic embolism in patients with nonvalvular atrial fibrillation and both prevention and treatment of venous thromboembolism. Despite these many advances, there still remain some gaps regarding the pharmacology and clinical relevance of the pharmacokinetics of these

drugs. Rivaroxaban is a Factor Xa-inhibitor agent that is a substrate for the hepatic cytochrome P450 3A4 (CYP3A4); it is mainly eliminated through renal permeability glycoprotein (P-gp) efflux transporter protein system. Dabigatran, instead, is not a CYP3A4 but a P-gp substrate. [2-3] A history of stroke accounts for about 30–40% of acquired epilepsy in the elderly, placing the concomitant use of antiepileptic agents and DOACs in a rather frequent situation. [3] The pharmacokinetics and pharmacodynamics of antiepileptic drugs are heterogeneous and complex and much of these aspects have been well studied both in in vitro and in animal models, but unfortunately little human research has yet been conducted. The induction of CYP3A4 activity by phenytoin has been clearly documented in humans, but P-gp induction has only been demonstrated in animals (Phase I studies).

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. [2-4] 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) [5-7] The approved dose regimen for rivaroxaban in VTE treatment is 15 mg twice daily for the first 3 weeks, and 20 mg once daily thereafter for the specified duration of therapy. [8-9]

This schedule was derived based on the fundamental pharmacological properties of Rivaroxaban, data from phase II dose-finding studies, pharmacokinetic modelling and randomised phase III clinical trials.

MATERIALS AND METHODS

Materials

Drugs and chemicals

Phenytoin and Rivaroxaban were procured from Matrix laboratories as a gift sample. All HPLC grade solvents (methanol and water) were procured from Finar chemicals Ltd., Ahmadabad. All chemicals used were analytical grade.

Animal study

Male Wistar rats (weighing 200-220 g) 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. (IAEC NO: IAEC/1657/CMRCP/T2/Ph D-16/68).

Study Design

The rats were grouped as follows:

Group I: Phenytoin alone in single dose/day in healthy rats.

Group II: Rivaroxaban alone in single dose/day in healthy rats.

Group III: Phenytoin 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 hours (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 1 min 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 200µ1 of mobile phase was injected for HPLC analysis.

For HPLC using Hypersil BDS C18, mobile phase comprising of methanol: phosphate buffer (pH 5.0) (50:50), flow rate of 1.0 ml/min and a detection wavelength of 215 nm using a UV detector. The retention time for phenytoin sodium, Rivaroxaban and phenobarbitone (Internal Standard) was found to be 3.97 min 5.12 and 6.90 min, respectively.

Standard calibration curve of Phenytoin and Rivaroxaban in rat plasma

Different concentration (0.05, 0.1, 0.5, 1, 5, 10, 20, 40 ng/ml) of Phenytoin, Rivaroxaban in plasma were prepared for calibration curve. The samples were treated as above for protein precipitation method and peak areas of Phenytoin and Rivaroxaban were noted down. The peak area ratios obtained at different concentrations of the Phenytoin, 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 24 hours, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The $AUC_{0-\alpha}$ was calculated using the formula AUC_{0-t} + [C_{last}/K] where C_{last} is the concentration in µg/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 Phenytoin, 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.

RESULTS AND DISCUSSION

In the present study, Phenytoin is completely absorbed after oral administration with peak plasma concentration of 7.24 ± 0.39 ng/ml after 3 hours of dosing on day 1. In combination with Phenytoin and Rivaroxaban on day 1, the peak plasma concentration of Phenytoin 7.14 ± 0.39 ng/ml occurred 3 hours 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 ± 1.03µg/ml occurred 4 hours after dosing on day 1, in combination with Phenytoin and Rivaroxaban on day 1. The peak plasma concentration of Rivaroxaban 4.12 ± 1.03 ng/ml occurred 2 hours after dosing. There was no significant difference in the peak plasma concentration levels, on day 8 of Phenytoin alone and with combination of Phenytoin with Rivaroxaban on day 8. Peak plasma concentrations are 8.24 ± 0.39 ng/ml and 8.14 ± 0.39 ng/ml, Rivaroxaban on day 8 and combination with Phenytoin concentrations are 7.02 ± 1.03 ng/ml and 4.12 ± 1.03 ng/ml respectively (results were showed in Table 1, 2, 3, 4 and Figure 1, 2, 3 and 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_{max}.. 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.

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

Parameters	Phenytoin alone	Phenytoin combination with Rivaroxaban
C_{max} (ng/ml)	7.24 ± 0.39	7.14 ± 0.39
t_{max} (h)	2 ± 0	2 ± 0
AUC_{o-t} (ng/ml/h)	63.45 ± 4.24	466.27 ± 4.52
AUC_{o-inf} (ng/ml/h)	78.82 ± 4.50	671.15 ± 5.85
$T_{1/2}$ (h)	4.56 ± 0.28	4.64 ± 0.09

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

Parameters	Phenytoin alone	Phenytoin combination with Rivaroxaban
C_{max} (ng/ml)	8.24 ± 0.39	8.14 ± 0.39
t_{max} (h)	2 ± 0	2 ± 0
AUC_{o-t} (ng/ml/h)	77.36 ± 5.38	81.18 ± 6.49
AUC_{o-inf} (ng/ml/h)	83.36 ± 7.63	89.49 ± 7.74
$T_{1/2}$ (h)	4.4 ± 0.24	4.08 ± 0.18

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

Parameters	Rivaroxaban alone	Rivaroxaban in combination with Phenytoin
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 Phenytoin day 8

Parameters	Rivaroxaban alone	Rivaroxaban in combination with Phenytoin
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

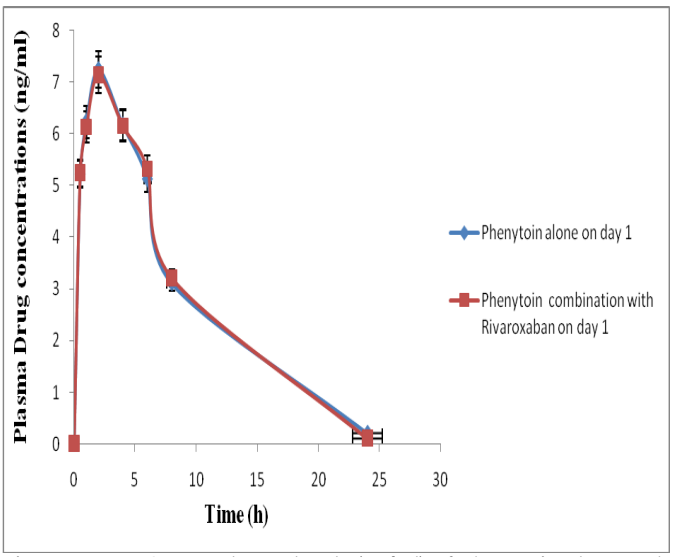

Fig. 1: Mean ± S.E.M, plasma levels (ng/ml) of Phenytoin alone and in Combination with Rivaroxaban on day 1

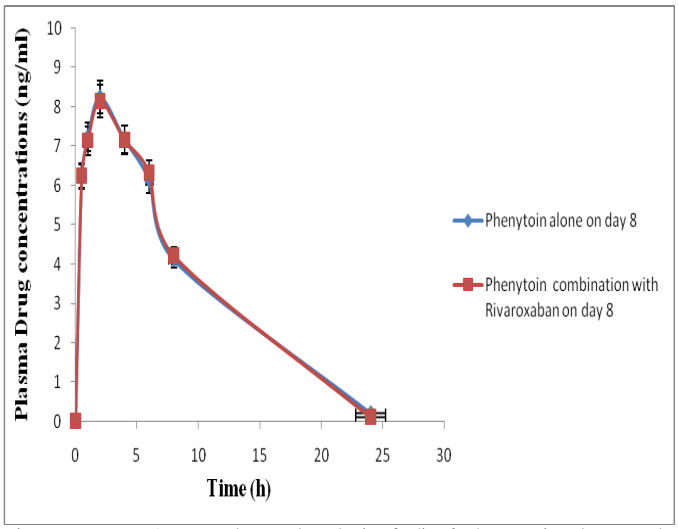

Fig. 2 : Mean ± S.E.M, plasma levels (ng/ml) of Phenytoin alone and in Combination with Rivaroxaban on day 8

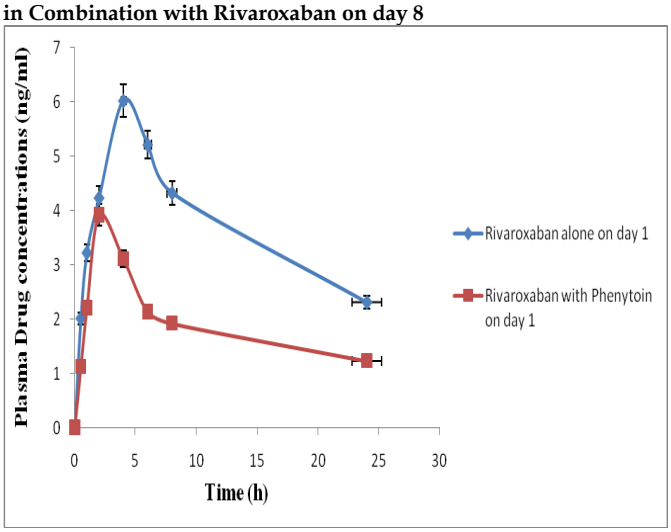

Fig. 3: Mean ± S.E.M, plasma levels (ng/ml) of Rivaroxaban alone and in Combination with Phenytoin on day 1

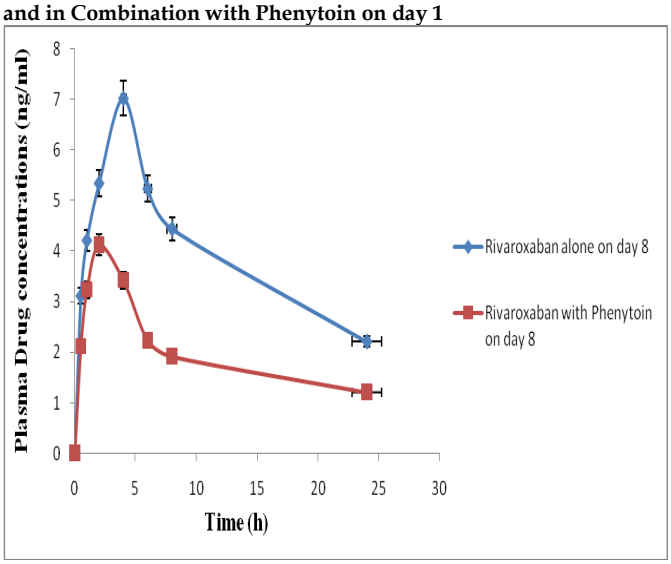

Fig. 4: Mean ± S.E.M, plasma levels (ng/ml) of Rivaroxaban alone and in Combination with Phenytoin on day 8

Phenytoin 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. Phenytoin 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.

From the present study the results were showed no significant difference in the t_{max} of Phenytoin alone and combination with Rivaroxaban on day 1 and day 8 respectively. There is a significant decrease in both C_{max} and t_{max} of Rivaroxaban in combination with Phenytoin on day 1 and day 8. Phenytoin is 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 pharmacokinetic study it was evident that the single dose of Phenytoin and Rivaroxaban individually and concomitantly treated shows statistically significant interactions in its pharmacokinetic parameters.

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HOW TO CITE THIS ARTICLE: Karnakar Reddy Y, Ramamohan Reddy T. Pharmacokinetic Interactions between Concomitantly Administered Phenytoin with Rivaroxaban. Int. J. Pharm. Sci. Drug Res. 2018; 10(5): 406-409. **DOI: 10.25004/IJPSDR.2018.100507**