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Original Research Article

Interaction of rabeprazole with phenytoin sodium: a prospective study

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ABSTRACT

Background: Phenytoin Sodium, a commonly prescribed anti-epileptic, with narrow therapeutic index, may interact with Rabeprazole, a commonly used Proton Pump Inhibitor (PPI), as both are metabolized by CYP2C19, potentially impacting bioavailability, therapeutic outcomes, and patient safety.
Methods: A total of 52 epileptic patients, previously stabilized on phenytoin, have now been prescribed Tab Rabeprazole for a minimum of 30 days and were included in the study after meeting the other inclusion criteria. On day-0, a blood sample was collected from these patients, and plasma phenytoin level was determined using High-Performance Liquid Chromatography (HPLC). Additionally, clinical evaluations and assessments of other routine laboratory parameters were conducted. The Follow-up evaluations was done on day-15 and day-30, replicating the procedures employed on day-0, including both clinical, laboratory assessments and plasma phenytoin level measurement using HPLC. All data was recorded in the case report form, and statistical analysis was done.
Results: The mean Phenytoin level exhibited a non-significant increase, rising from 15.49 µg/ml on day-0 to 15.57 µg/ml on day-15 and further to 15.75 µg/ml on day -0. Notably, there was no change in epilepsy outcomes concerning both seizure frequency and adverse effects. Additionally, there were no statistically significant changes observed in epilepsy control, SBP, DBP, and routine laboratory parameters, including haemoglobin, TLC, DLC, platelet count, serum albumin, serum globulin, serum bilirubin, SGOT, SGPT, serum urea, serum creatinine, and BSL (random).
Conclusions: The co-administration of rabeprazole with Phenytoin resulted in a non-significant increase in Phenytoin levels, while maintaining stable control of epilepsy.

Keywords: HPLC, Pharmacokinetics, Phenytoin, Rabeprazole

INTRODUCTION

Epilepsy is a chronic neurological disorder, which affects people of all ages. It constitutes a substantial portion of the global disease burden. A "seizure" is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain.[1] Epilepsy afflicts approximately 70 million individuals worldwide, with nearly 12 million of those affected residing in India. This sizable number represents almost one-sixth of the global epilepsy burden.[2] Amongst numerous newer medications for the treatment of epilepsy available, phenytoin sodium remains a cost-effective and widely utilized choice. Even in tertiary care hospitals, it is noteworthy that a substantial majority, ranging from 80% to 90% of epileptic patients achieve stabilization with phenytoin at appropriate doses.[3,4] The pharmacokinetics of phenytoin sodium is influenced by several key factors, including its plasma protein binding, non-linear elimination kinetics, and metabolism by hepatic CYPs. It's also important to note that Phenytoin has a narrow therapeutic index.[5] Consequently, even minor variations in Phenytoin's dosage or blood concentration can have critical implications, potentially

resulting in therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity to the patient.[6] Proton pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion available, and they are effective for treating all acid-related disorders and are commonly co-prescribed prescribed with phenytoin.[7] Rabeprazole is a benzimidazole proton pump inhibitor. Rabeprazole covalently binds with and inhibits gastric parietal cell proton pump (H+/K+ ATPase.[8] Rabeprazole is effective in the healing of erosive GERD, duodenal ulcer and gastric ulcer, also useful in Zollinger-Ellison syndrome.[9] It is a frequently prescribed and widely used proton pump inhibitor (PPI). Cytochrome P450s are a super family of heme-containing enzymes found in most living species. In humans, at least 57 cytochrome P450s have been identified, the main functions of which include biosynthesis of body steroids and metabolism of endogenous and xenobiotic compounds, including drugs and toxins.[10] The primary enzymes involved in metabolism of phenytoin are the cytochrome P450 (CYP) isoforms CYP2C9 and CYPC19, while Other CYP isoforms may also play a minor role.[11] Rabeprazole is metabolised in body non-enzymatically as well as enzymatically primarily by CYP2C19 and secondarily by CYP3A4.[12] As these two drugs are substrates for the same enzyme i.e., CYP2C19, there is a possibility of increase in bioavailability of Phenytoin Sodium which may affect the therapeutic outcome and possibility of Adverse drug reactions. An animal study shows that when esomeprazole is co-prescribed with Phenytoin, esomeprazole alters the pharmacokinetics of phenytoin to a significant level, since it is a competitive inhibitor of CYP2C9 and CYP2C19.[13] Humphries et al conducted study on healthy volunteers who were on Phenytoin along with Rabeprazole. This study showed that there is no effect of Rabeprazole on Phenytoin Pharmacokinetics.[14] In the view of above background, the present study is planned to see any changes in therapeutic drug concentration of phenytoin sodium when it is co-prescribed with rabeprazole.

METHODS

The prospective, observational study was conducted during 1st January 2019 to 30th June 2020 in Department of Pharmacology in collaboration with Department of Medicine in Government Medical College, Aurangabad. The study aimed to examine the plasma concentration of phenytoin sodium when co-administered with rabeprazole and to assess the impact on epilepsy outcomes in such co-administration.

Inclusion criteria

In this study, we included diagnosed cases of epilepsy that were stabilized on phenytoin sodium and co-prescribed with 20 mg of rabeprazole once a day for a minimum of one month. Patients of either sex, aged over 18 years, who were willing to provide informed written consent were eligible for inclusion.

Exclusion criteria

Patients with a known history of chronic hepatic or renal disease, pregnant patients, those with a history of any hypersensitivity reaction to the aforementioned drugs, and those unwilling to give informed consent or follow up were excluded from the study.

After Institutional Ethics Committee permission for the study, a total of 52 epileptic patients, previously stabilized on phenytoin, have now been prescribed Tab Rabeprezole for a minimum of 30 days and were included in the study after meeting the other inclusion criteria. On day 0, a blood sample was collected from these patients, and the plasma phenytoin level was determined using High-Performance Liquid Chromatography (HPLC). Additionally, clinical evaluations and assessments of other routine laboratory parameters were conducted. Patients' demographic characteristics, Baseline clinical & routine laboratory data was recorded in Case Report Form (CRF). The patient continued his AED regimen with newly prescribed tab Rabeprazole. Patient was again evaluated on day 15 and Day 30 and all the procedure as on day 0 (i.e., plasma phenytoin level measurement using HPLC, clinical evaluation, and laboratory investigation) were repeated. Thus, patient's evaluation time points were at day 0, day 15 and Day 30. All the data was recorded in case report form. Paired t test was applied for statistical analysis, and the results were evaluated.

TDM METHOD

TDM buffer solution for mobile phase

27.2 gm of potassium dihydrogen phosphate (KH2PO4) +1000 ml of distilled water. Adjust pH to 6.00 by adding 1M NaOH solution [0.2 M KH2PO4 buffer at pH 6.0] (27.2 gm for 1000 ml D.W. or 13.6 gm for 500 ml of D.W.) Preparation of NaOH solution: Add 3-4 pellets of NaOH in 10 ml D.W.

Table 1: Preparation of mobile phase.

	Buffer	D.W	MeOH	ACN
Ratio	1.64	43	37	20
for 500 ml	8.2 ml	215 ml	185 ml	100 ml

Preparation of stock standards

Preparation of stock phenytoin (PHT) – 1 mg/ml, 10mg of Phenytoin in 10 ml of Methanol, shake it well.

Preparation of stock internal standard (SIS) – 1 mg/ml

5-ethyl 5-para tolybarbituric acid (1mg/ml) (Weigh 10 mg of 5-ethyl tolybarbituric acid and dissolve it in 10 ml of MeOH. Take 1 ml of it and dissolve this in 9 ml of MeOH. Which will give 100 mcg/ml solution. Use this solution in preparation of is 10 mg of SIS in 10 ml MeOH, Shake it well.

Preparation of internal standard (IS)

6.5ml of D.W. + 0.5 ml of SIS (from step 4) = 7ml of stock- Vortex

Preparation of internal standard working

Dilution of Acetonitrile (ACN) in Ratio of 1:10,1 ml (from previous 7 ml sample of IS) + 9 ml of ACN.

Preparation of plasma standard

Stock: - 2.0 ml = 1750 µL blank plasma + 100 µL of PBT stock + 100 µL PHT Stock + 50 µL CBZ stock (Use Hamilton Syringe). STD-I: - 0.9 ml blank plasma + 0.1 ml of Stock (Plasma standard) – Vortex, STD-II: - 0.8 ml blank plasma + 0.2 ml of Stock (Plasma standard) – Vortex. QC-Reconstitute the sample in 4ml of DW – take 0.5 ml.

Preparation of *internal standard (IS)*

6.5ml of D.W. + 0.5 ml of SIS (from step 4) = 7ml of stock- Vortex.

Preparation of *internal standard working*

Dilution of Acetonitrile (ACN) in Ratio of 1:10, 1 ml (from previous 7ml sample of IS) + 9 ml of ACN

Preparation of plasma standard

Stock: - 2.0 ml = 1750 µL blank plasma + 100 µL of PBT stock + 100 µL PHT Stock + 50 µL CBZ stock (Use Hamilton Syringe). STD-I 0.9 ml blank plasma + 0.1 ml of Stock (Plasma standard) – Vortex, STD-II 0.8 ml blank plasma + 0.2 ml of Stock (Plasma standard) – Vortex, QC: - Reconstitute the sample in 4ml of DW – take 0.5 ml.

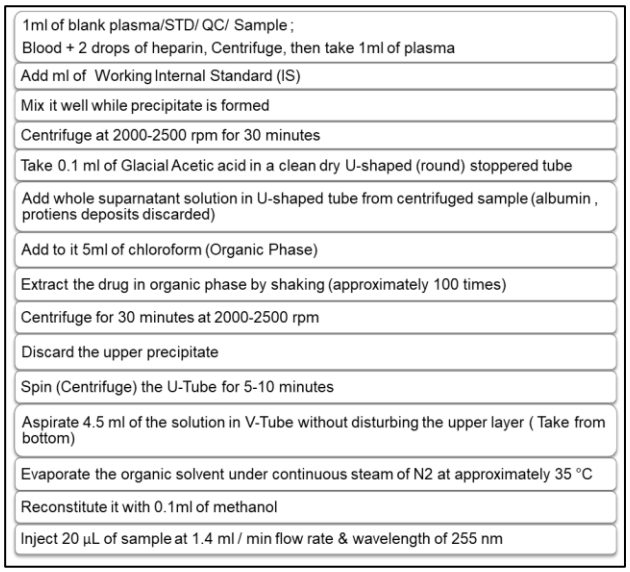

Figure 1: Extraction procedure.

Therapeutic ranges

PBT = 10-40 µg/ml, PHT = 10-20 µg/ml, CBZ = 04-12 µg/ml.

Preparation of conditioning solution for column wash

DW (100): MeOH (100)

Preparation of mobile phase

Buffer (16.4): D.W. (430): MeOH (370): AC (200) = 1000 ml Buffer (8.2) : D.W. (215): MeOH (185): AC (100) = 500 ml

HPLC setting

Column: C18**,** Flow Rate: 1ml/min**,** Injection Volume: 10 µl**,** Temperature: 55°C**,** Detection: UV @ 255 nm**,** Instrument: La Chrome Elite.

RESULT

A total of 52 eligible patients fulfilling the inclusion/exclusion criteria were selected. Out of 52 patients 29 were male and 23 were female. The study parameters were assessed on day 0 with Tab Phenytoin only and on day 15 and day 30 after receiving Tab Phenytoin along with Tab Rabeprazole 20 mg once a day for one month. The statistical assessment was done by applying paired t-test to obtain quantitative data. Among total 52 patients enrolled, 29 were female (56%) & 23 were male (44%) as shown in Table 2 with male to female ratio of 1.26. As shown in Figure 2, maximum number of patients between age group of 18-30 years (38.48%) followed by 31-40 years (28.84%).

Table 2: Number of patients by gender.

S. no.	Gender	Number	%
1	**Male**	29	56
2	**Female**	23	44

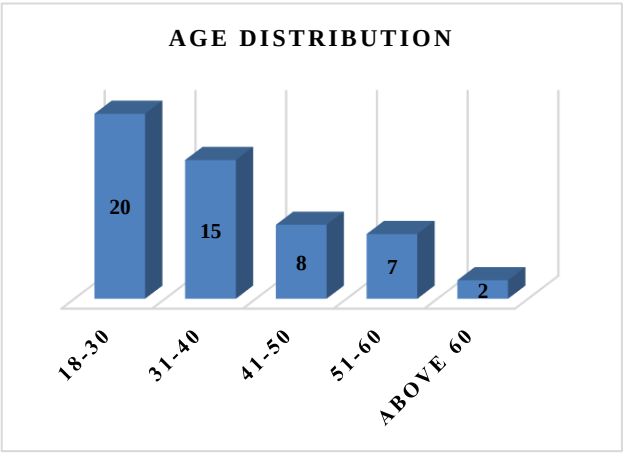

Figure 2: Number of patients by age (in years).

Parameter for assessment of effect on pharmacokinetics

As shown in Table 3 and Figure 3, The mean Phenytoin level on day 0 was found to be 15.4994 µg/ml, which increased to on Day 15 to 15.5792 µg/ml and further to 15.7538 µg/ml on Day 30. The paired t-test was applied to day 0 and day 15 mean phenytoin level & then to day 0 and day 30 mean phenytoin level with confidence interval of 95% and degree of freedom of 51. The difference was found to be statistically not significant. (The two-tailed P value for pair 1 equals 0.3021 and the two-tailed P value for pair 2 equals 0.0122 i.e. p>0.05 for both pairs).

Table 3: Effect on phenytoin level.

		Mean (µg/ml)	N	Mean std. deviation (σ)	Std. error mean
Pair 1	Phenytoin Day 0	15.4994	52	1.74706	0.24227
	Phenytoin Day 15	15.5792	52	1.51460	0.21004
Pair 2	Phenytoin Day 0	15.4994	52	1.74706	0.24227
	Phenytoin Day 30	15.7538	52	1.62717	0.22565

Parameters for assessement of effect on epilepsy outcome

All the subjects included in the study were evaluated on day 0, day 15 & day 30 for epilepsy outcome. Change in seizure frequency, development of any study drug associated toxicity features and any significant clinical remarks were noted. As shown in Table 4, out of total 52 subjects, no subject has shown change in seizure frequency or any toxicity features.

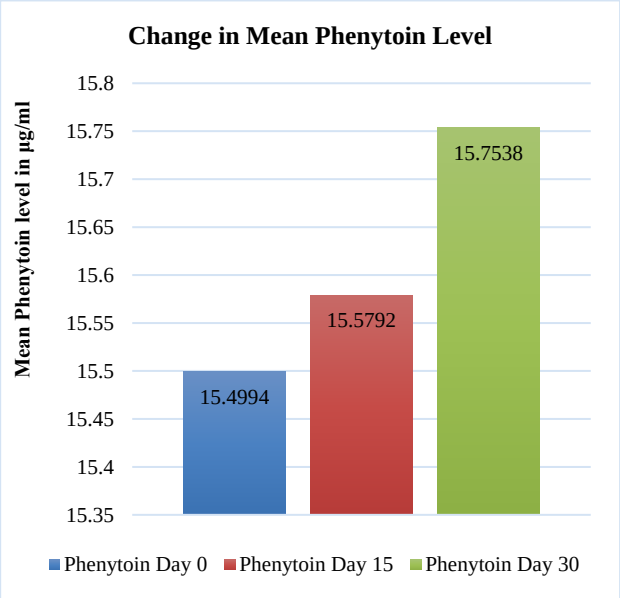

Figure 3: Change in mean phenytoin level.

Table 4: Epilepsy outcome parameters.

Parameter	Frequency of subjects with positive response	Frequency of subjects with negative response	Total subjects assessed
Change in seizure frequency	Nil	52	52
Development of any study drug associated toxicity features	Nil	52	52
Any significant clinical remarks	Nil	52	52

Routine laboratory parameters

Systolic and diastolic blood pressure and routine laboratory parameters like hemoglobin, TLC, DLC, platelet count, serum albumin, serum globulin, serum bilirubin, SGOT, SGPT, serum urea, serum creatinine and blood sugar level (random) were evaluated by comparing day 0 level with day 15 level and day 0 level with day 30 level. Paired t-test was applied, and results were found to be statistically non-significant.

DISCUSSION

In this study, serum phenytoin level was increased on day 15 i.e. 15.5792 µg/ml and further 15.7538 µg/ml on day 30 compared to day 0 i.e. 15.4994 µg/ml. Though this difference was statistically not significant, it could have broader implications concerning the toxicity of phenytoin, given its narrow therapeutic index. Metabolism of phenytoin is non-linear within the therapeutic range because the enzyme system responsible gradually becomes saturated at relatively low plasma phenytoin concentration (within the therapeutic range), resulting in a progressive decrease in the rate of elimination of Phenytoin as the dosage is increased. The decrease in expression of CYP2C19 or its inhibition by rabeprazole decreases Phenytoin clearance. As it is possible to predict, whether two drugs are likely to interact with each other or not based on the CYP level by knowing: Which CYP isoform(s) is/are mainly responsible for the metabolism of the drugs. The relative contribution of the CYP isoform(s) to the total metabolism of the drugs. (c) the relative affinities of the drugs for the CYP isoform(s). The relative concentrations of the drugs in hepatocytes as judged from plasma concentrations.

If two drugs are metabolized by the same CYP isoform, a competitive inhibition can be predicted, and the metabolism of the drug with the least affinity for the enzyme will probably be inhibited. Because the main CYP isoforms involved in the metabolism of rabeprazole

are CYP2C19 and CYP3A4, a drug–drug interaction would occur with drugs transformed mainly by either of these two CYP isoforms.[15] PPIs undergo extensive metabolism by cytochromes P450 (P450s). All PPIs inhibit various CYP450s. Zvyaga et al demonstrated that, of the P450s tested for inhibition by PPIs, the most potent inhibition was observed with CYP2C19-catalyzed (S)-mephenytoin 4'-hydroxylase activity.[16] M VandenBranden et al also demonstrated that Rabeprazole has potential to inhibit the metabolism of CYP2C19 substrates, though less compared to omeprazole.[17]

According to Xue-Qing Li et al, all PPIs are inhibitors of Phenytoin metabolising enzyme CYP2C19.[18] It is also evident in the following Table 4 derived from study by Sweeney et al.[19] Rabeprazole, as member of PPI family also inhibits enzyme CYP2C19. All of PPI are inhibitors of CYP2C19 enzyme to varying degrees. Our study shows that the possibility of enzyme inhibition by Rabeprazole is a cause for slight increase in serum Phenytoin level. In this non-interventional observational study, a single pharmacokinetic parameter i.e., mean serum Phenytoin level was determined.

In our study, as shown in Table 3, neither change in seizure frequency pattern nor development of any study drug associated toxicity features were observed in any study subject during the study duration. Various studies indicated that within therapeutic range of phenytoin, there is maximum therapeutic efficacy and minimum probability of toxicity.[20,21] In our study, all the subjects had maintained the Phenytoin levels in the therapeutic range for complete duration of study. Hence, there is absence of therapeutic failure and toxicity features among the study subjects. However, with higher range of phenytoin levels, whether Rabeprazole by inhibiting CYP2C19 enzyme increases the levels of phenytoin or not, cannot be commented. Laboratory investigations like BSL, WBC, platelet count, differential WBC count, serum protein, serum total bilirubin, SGOT, SGPT, blood urea and serum creatinine did not show any significant change.

Limitations

This study has some limitations first, it did not assess other pharmacokinetic parameters, which could have provided a more comprehensive understanding of the drug interactions. Second, the number of participants was limited, potentially affecting the generalizability of the findings. Lastly, the study lacked a monitoring system for patient compliance, leading to variability in adherence that could influence the study outcomes.

CONCLUSION

While our evaluation focused solely on serum phenytoin levels as the primary pharmacokinetic parameter alongside epilepsy outcomes and other laboratory tests. In light of our study's results, which indicate a slight but not statistically significant increase in phenytoin concentration with Rabeprazole, healthcare practitioners should exercise caution when prescribing Rabeprazole alongside Phenytoin.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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