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Research Article

Case series on the Clinical evidence of Phenytoin toxicity: Is Ranitidine a cause?

SADAGOBAN G.K [1], MEDAVENKATASUBBAIAH[2], ARUN KANNIYAPPAN PARTHASARATHY, SWATHI SWAROOPA BORRA[1*]

[1]lecturer, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamil Nadu, India.

[2]Associate Professor, Department of Pharmacy Practice, P Rami Reddy Memorial College of Pharmacy, Kadapa, Andhra Pradesh, India.

[3]Assistant Professor, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamil Nadu, India.

*Corresponding Author

Email:swasasree@jssuni.edu.in

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ABSTRACT

Purpose: Phenytoin toxicity can result with the overdose, change in frequency and alteration in physiology and drug-drug interactions. The manifestations of Phenytoin toxicity include confusion, diminished consciousness, ataxia, coma, seizure attacks, etc. and the severity is more with parenteral administration. There are very few published data reveal the significance of drug-drug interaction between Phenytoin and Ranitidine. Mere clinical evidence-based literature on Phenytoin and Ranitidine interaction is not enough for the interventions, through these reports we tried to associate Phenytoin toxicity with Ranitidine co-administration. **Objective:** To determine the interaction between ranitidine and phenytoin through these case series. **Method**: Collected five suspicion cases of ranitidine and phenytoin interaction and thorough literature review, Chart review and patient interview collected to find association of drugs. **Results**: All five patients have developed seizures during their course of therapy along with other Phenytoin toxicity like Central Nervous System (CNS), Gastro Intestinal Tract (GIT) and skeletal muscle manifestations. In all cases other possible cause of these manifestations were also assessed and these were suspected to be due to interaction with the Ranitidine. One patient went to higher centre and remaining patients have shown recovery from after drug/s withdrawal. **Conclusion**: Though these data may not be sufficient enough to confirm the adverse drug interaction, it helps in strengthening the literature of drug-drug interaction between Phenytoin and Ranitidine. This may sensitise the prescribers in generating supporting data to take necessary actions in the patients.

Impact on Practice Statements: Prevents unintended and unwanted effects on patient and healthcare system

Keywords: Phenytoin, Ranitidine, Drug Interaction, Toxicity.

INTRODUCTION

Phenytoin is one of the most widely used drugs among all anticonvulsants for the management of seizures and included in the World Health Organization's Essential Drug List (EDL). On the other hand, due to narrow therapeutic ratio, precarious metabolism, poor solubility, inter-subject variation and saturation elimination kinetics, Phenytoin warrants dosage adjustments based on the measured concentrations in the blood, failing which might result in toxicity. Such toxicity may be further augmented if administered with the drugs those inhibit the metabolism and in patients with co morbidities like hepatic disorders. Former is an important issue in the health care system which can be explained through pharmacokinetics and pharmacodynamics, but, the majority are of metabolic enzymes alterations in the liver i.e. either induction or inhibition of the responsible enzymes by the interacting drugs. [1-4]

The clinical manifestations of Phenytoin toxicity include nausea, vomiting, CNS dysfunction nystagmus, ataxia, coma and seizures. In severe cases, it leads to arrhythmias, hypotension, slurred speech, lethargy, hypersensitivity reactions and toxic epidermal necrolysis etc., the severity of these effects may also depend on the route and dose. [3]

Phenytoin is primarily metabolized by by CYP2C9 (90%) and partly by CYP2C19 (10%) to its major inactive metabolite 5-(para-hydroxyphenyl)-5-phenylhydantoin (p-HPPH). [5]

Liver diseases, changes in albumin configuration, genetic polymorphism of metabolising enzymes or drugs influencing on metabolising enzymes may contribute to the phenytoin toxicity as it is

highly protein-bound drug and the majority of the drug metabolizes through the liver. During phenytoin therapy, the slight inhibition of drug metabolism may considerably increase the phenytoin drug concentration. The dose required to produce a concentration in the accepted therapeutic range is very close to that which will cause intoxication. Drugs which alter the activity of these enzymes may affect the metabolism of the Phenytoin and cause toxicity. [4, 6] Many Significant and non-significant Drug-drug interactions has been reported with phenytoin. Out of which, significance of phenytoin and ranitidine interaction is uncertain and controversial. [7]

In majority of the patients, H2-receptor blockers (HRBs) are proved to be highly effective for various acid-peptic diseases. [8] Studies showed that the HRBs interact with microsomal metabolism of many drugs and results in the increased plasma concentrations, and the impact of this will be more with narrow therapeutic index drugs like, Phenytoin. [9-11]

The role of histamine blockers especially Cimetidine interaction was well documented in the literature, [6] but there is a controversial evidence on the Ranitidine role. [7] The present series of cases are mainly focussed on the clinical evidences of the Phenytoin toxicity due to adverse interaction with Ranitidine.

Aim of the study

To determine the association of Drug-drug interaction between Ranitidine and Phenytoin through these case series

Method

Various sources of data, hospital clinical records, patient and care giver interview, was done to collect detail history of the event occurred and discussed with the physician for changes in the therapy. We have started this study after receiving Informed Consent from all patients.

Case description

Case#1

A 28 years old woman was presented to the Intensive care unit with a seizure disorder. Her symptoms during seizure episode were with headache, rolling of tongue, upper gastric pain and have become unconscious; she is a known case of generalized tonic-clonic seizure since 1 year and has 2 episodes of seizures with 3 months interval. On examination, the patient was unconscious, disoriented, afebrile, and not paralyzed. Her abdomen was soft. Upper and lower limbs deficits were appreciated on neurological examination. On investigation, all her laboratory parameters were found to be normal. On the day of admission she has been given with Phenytoin 100 mg intravenously 8th hourly, Ranitidine 50 mg intravenously 12th hourly, Intravenous fluid Ringer Lactate (RL) 500ml once a day. On third day the patient developed one more episode of the seizure with twitching of eye, nystagmus, slurred speech and twitching of muscles, ataxia. Suspecting phenytoin toxicity, the phenytoin has been stopped and immediately the patient was given with Midazolam 4 mg intravenously. The seizures were controlled with midazolam and the patient condition improved slowly after four days of Phenytoin discontinuation. The patient was discharged with oral Sodium valproate, Ranitidine and Vitamin B complex tablets.

Case#2

A 14-year-old girl admitted in the general ward with the first episode of tonic-clonic seizures in the school hostel. Her vitals were normal. On physical examination, she complained of right shoulder movements were a little painful. She has a family history of seizures; her father is a known case of epilepsy. On the day of admission, the patient was given with intravenous fluid Dextrose Normal Saline (DNS) 1000ml, Tablet Phenytoin 200 mg at bed time, Tablet Ibuprofen 200 mg 8th hourly, Tablet Ranitidine 150mg 12th hourly and meanwhile physician sought the orthopedic surgeon opinion and CT brain report; no abnormalities were observed by the orthopedic surgeon and CT Brain. No abnormalities were found in laboratory results. Once the patient condition recovered, she got discharged with same medications for one month period except ibuprofen and advised to review after 1 month. After 2 weeks of treatment the patient readmitted in the hospital with severe shoulder pain followed by an episode of seizures, and hypotension. Based on clinical signs it was suspected as phenytoin toxicity and phenytoin has been stopped abruptly for recovery. Midazolam was given for controlling seizures, After 48 hours of close observation the patient was discharged at her own request for moving toward a higher center for treatment.

Case#3

A 21 years old male stage 4 Chronic Kidney Disease (CKD) patient got admitted in Intensive Care Unit (ICU) with one episode of seizure. He is on regular dialysis since 5 months. No family history of seizure. On examination patient was conscious and coherent, his vitals were normal and lab investigations showed elevated RFT . Upon admission, the patient had given Phenytoin

400 mg in 250 ml in Normal Saline (NS) infusion for 1 hour, DNS 500ml third hourly, Ranitidine 50 mg intravenously 12th hourly (Table 1). On the second day, the patient complained of severe abdominal pain, nausea, vomiting and headache; the same medications were continued by adding Metronidazole 500mg intravenously stat, Dicyclomine 8 mg intravenously stat. On the third day, he complained headache again, on the same day evening patient had an episode of seizure, disorientation. Suspecting Phenytoin as a cause, it was stopped and the patient was discharged next day with Tablet Sodium Valproate 400mg 12th hourly, and Tablet Amlodipine 5mg 12th hourly. Advised the patient to come for review after 15 days

Case#4

A 47 year old female patient admitted in hospital with one episode of seizure with drooling of saliva, tongue bite and she was a known case of seizure disorder for 13 years and on Phenytoin 100mg 12th hourly and sodium valproate 200mg once in 24 hours for the same period; Tablet Ranitidine 150 mg 12th hourly since one month for her gastric manifestations. Serum glutamic oxaloacetic transaminase (SGOT) (187U/L), Serum glutamic pyruvic transaminase (SGPT) (105U/L) and Pus cells (8-10/hpf) in Urine showed elevation. On admission the patient has been administered with Inj. Phenytoin 400mg in 100 ml NS, T. Phenytoin 100mg 12th hourly, T. Sodium Valproate 8th hourly, T. Ranitidine 150mg 12th hourly. On second day patient developed a seizure episode involving Right upper limb with prodromal symptoms and loss of consciousness. Infusion Phenytoin has been stopped and continued with T. Phenytoin, T. Ranitidine, and T. Sodium Valproate and the patient has been complained of giddiness and confusion on third day with no signs of improvement in previous complaints. Next day phenytoin was replaced with the T. Carbamazepine 200mg 12th hourly and ranitidine was stopped. The medication has been continued for 2 days and the patient has shown recovery and has been discharged with sodium valproate 200mg once in a day and carbamazepine 200mg 12th hourly.

Case # 5

46 years female Patient admitted with one episode of seizures, breathlessness and hematemesis. On examination she was semiconscious, her Blood Pressure (BP) was 130/90 mmHg and Pulse Rate (PR) of 82 beats/minute. She is a known case of Type 2 Diabetes Mellitus (T2DM) for the past 1 year and on Metformin 500 mg twice a day. Diagnosis was made as Type 2 DM and Lower Respiratory Tract Infection (LRTI). On day of admission She was prescribed with Injection Ranitidine 50 mg IV twice a day, IV fluids RL 1 pint at 100 ml/hr, and injection Phenytoin 100 mg in 100ml NS and T. Phenytoin 200mg HS. On second day the patient had an episode of seizure with one episode of vomiting and BP was reduced to 80/60 mmHg, PR was 72 beats/m. Phenytoin was replaced with Inj Diazepam 10 mg BD, and ranitidine was replaced with INJ. Pantaprazole 40mg BD along with INJ. Ondansetron 8 mg BD and IV fluids RL 1 pint and NS 2 pint at 100 ml/hr for two days. On third day no improvement was seen, BP was 90/50 mmHg, PR: 62 beats and continued the same treatment. On day 4 Laboratory data was found to be normal except Post Prandial Blood Sugar (PPBS) of 248 mg/dL and the patient BP was improved on fourth day to 110/70 mmHg, PR was 98 beats/m. The medication continued and added Tablet Metformin 500mg BD, Capsule Omeprazole 20 mg BD, Tablet Domperidone 10 mg BD, Tablet cetrizine 10 mg at night time and Salbutamol Nebulizer 8th hourly for mild breathlessness. On day 5, patient BP was 120/80 mmHg, PR was 76 beats/m and patient was treated with the same drugs and IV fluids were stopped and tablet Azithromycin 500 mg once in a day was added. No further seizure attacks and patient got discharged with same medication.

DISCUSSION:

In our observation we found five cases with phenytoin toxicity between the age group of 14 to 50 years with Generalized Tonic Clonic Seizures (GTCS) and one with uremic seizures. The common finding seen in all the cases was administration of phenytoin and ranitidine together. In the first case, Administration of Phenytoin with Ranitidine developed seizure, slurred speech, and muscle twitching after four hours of Ranitidine and Phenytoin administration. Immediately Midazolam was administered intravenously and observed that these fresh complaints were suspected as drug-induced, and analysis was done to find the causative agent and on discussion with prescriber, it was confirmed as Phenytoin toxicity and the next dose of Phenytoin was skipped and further evaluation was done to find out the reasons for its toxicity. In this case, we found an interacting drug i.e. Ranitidine in the prescription and this drug has the potential to increase the plasma concentration of Phenytoin by decreasing its metabolism mediated by CYP enzymes in the Liver. In support of this, we have observed the improvement in the patient's condition upon drug withdrawal. Study conducted by Simon Craig stated that the seizures occurred

due to phenytoin toxicity can treated with the Benzodiazepines, [3] other studies also demonstrated the ranitidine interaction and Phenytoin toxicity. [11-13]

Second situation patient experienced second seizure attack after 48 hours along with augmented shoulder pain even though the patient is on analgesic therapy i.e. Ibuprofen. And her BP is very low. With available information we tried to analyze the reasons for the re-occurrence of seizures and augmented shoulder pain i.e. skipping of Phenytoin dose, right-sided sleeping, immobility of hand due to cannulation, etc., but there is no evidence of these issues as the patient is compliant with the prescription, no stress on the right shoulder and cannulation was done on her left cuboidal vein and her blood pressure (BP) was reduced from 110/70 mmHg to 90/60 mmHg. So, we suspected it as Phenytoin toxicity and through further evaluation we suspected this condition is may be due to the negative consequence of co-prescription of Ranitidine as like in the first case but route and dose are different. In this case also as that of in case 1, we found the interacting drugs i.e. Ranitidine and Phenytoin. In support of this, we have observed the improvement in the patient's condition after replacement of phenytoin with Midazolam. A case report stated that in the patient with phenytoin usage regular follow up should be done to assess compliance and---------- response to therapy. Monitoring of serum phenytoin levels and ADRs should be done even when the seizure is under control to find out any toxic concentrations in the blood. [14]

In 3rd case the patient had developed seizures for the first time because of his kidney damage, and his renal function tests were also found to be abnormal at the time of admission and confirm the severity of the problem. On the day of admission patient was infused with Phenytoin 400 mg stat, followed by 100 mg intravenously and so, total dose given on the day of admission was 600 mg, from the second onwards 100 mg on 8th hourly basis for next two days along with other medications was administered. On 3rd day evening patient had developed seizures and prescriber stopped the Phenytoin and observed, on 4th day patient was apparently normal and discharged with oral Sodium Valproate, which gives the evidence for the Phenytoin toxicity and on evaluating the reasons for the toxicity,

we found multiple risk factors, such as patient is known CKD (which is having little importance according to the **Victoria Títoff et al.**, [17] where they stated that the excretion of Phenytoin through the kidney is very less ii.e. < 5% of which may not require an dose adjustments in CKD), administered with 600 mg of Phenytoin on the first day along with ranitidine from the first day at the same time intervals, which is suspected to increase the Phenytoin plasma levels and another interacting medication i.e. infusion Metronidazole 500 mg stat, which is also alters the metabolism and increases the Phenytoin plasma concentration. A healthy volunteer study conducted by Blyden GT et al., stated the impaired Phenytoin clearance and increased half-life due to co-administration with Metronidazole. [15]

This is an old case of epilepsy has been taking antiepileptics since 13 years along with the antiulcer drug for one month and we observed elevation in her liver enzymes, which is suspected to be drug induced, as antiepileptics can cause dose dependent elevation in the liver enzyme with or without causing hepatotoxicity. [18] On admission in this hospital due to seizure attack, patient had received the same therapy for first two days, on second day she had developed 2nd seizures along with neurological manifestations (prodromal symptoms), though she is on two antiepileptic medications. Her neurological symptoms were subsided after the discontinuation of Phenytoin and ranitidine and no further seizure attacks were observed during her hospital stay. The reasons for re-occurrence of seizures in this case are might be suspected to be hepatic pathology and usage of interacting drug i.e. ranitidine from one month this will increase the phenytoin levels and has the potential to cause toxicity.

In the final case, the patient is a known type 2 diabetes mellitus since one year and on oral Metformin therapy, who had developed seizures for the first time and received both oral and parenteral phenytoin and ranitidine on admission. On second day of the treatment patient had developed seizures and her blood pressure was fell down from 130/90 mmHg to 80/60 mmHg, upon cessation of phenytoin and ranitidine her blood pressure came to normal. Apart from other cases this patient had shown cardiac manifestations of phenytoin toxicity i.e. hypotention

These case reports were based on the clinical evidence of Phenytoin toxicity, and on finding the reasons for this toxicity. In all three cases recurrence of seizures after Phenytoin administration was observed along with other clinically relevant manifestations. With thorough analysis, we found some potential factors which would be the reason for the Phenytoin toxicity, which includes:

1. Co administration of Ranitidine in all three cases at same time, literature suggests that histamine blockers like cimetidine and ranitidine can increase plasma concentration of Phenytoin. [6, 11, 16]
2. Co administration of Metronidazole, which is also having the same properties like that of former drug, this become a synergistic effect on Phenytoin concentration. [15]
3. Polymorphism of CYP2C9, CYP 2C19, and CYP3A4, as per literature it is evidenced that the South Indian population especially Tamilians has this polymorphism than rest of India. [1]
4. Co morbidities (CKD, MUSCLOSKELETAL PAIN)
5. Chronic usage of Phenytoin along with sodium valproate and hepatic pathologic evidences.

As prescribers have taken necessary medical measures in time, fortunately no patient have developed severe problems, morbidity and mortality. Unintentional Phenytoin poisoning or self-poisoning only requires clinical observation and supportive care. [3]

CONCLUSION:

Case reports are primary source of evidence and signal generation. These cases confirm the toxicity of Phenytoin with co administration of ranitidine, which further has more clinical significance in presence of other co morbidities and drugs. There may be hidden risk factor, polymorphism and warrants genetic analysis to confirm this factor. Plasma concentrations need to be measured at the time of clinical symptoms to confirm the toxicity due to DDI. This study report triggers the healthcare professionals to take necessary precautions in co prescribing of Ranitidine and other interacting drugs like Metronidazole along with phenytoin and strict dose calculations in altered physiological states. Further studies with more sample size are required to confirm/strengthen our study results.

Conflicts of Interest

No Conflict of Interest

Compliance with Ethical standards

Informed consent form is obtained from the patients

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Table 1: Patients Characteristics

Patient	Age	Sex	Epilepsy type and history	Medication history	Co-morbid condition
1	28	F	GTCS since 1 year	Phenytoin	NIL
2	14	F	GTCS Newly Diagnosed	NA	NIL
3	21	M	Hemodialysis induced seizure Newly Diagnosed	NA	Stage 4 CKD
4	47	F	GTCS since 13 years	Phenytoin and Sodium Valproate	NIL
5	46	F	GTCS Newly diagnosed	NA	T2DM

[*F-Female, *M-Male, **GTCS-Generalised tonic clonic seizures, **T2DM-Type2 diabetes mellitus, ** CKD-Chronic kidney disease, * NIL-Nothing, *NA-Not available]

Table 2: Details of Five cases with phenytoin toxicity events observed

Case	Symptoms at the time of admission	Phenytoin		Duration (Days)	Ranitidine		Duration (Days)	Events observed	Other possible causes of the toxicity	De-challenge
		Dose and Frequency	Route		Dose and Frequency	Route				
1	Headache, loss of consciousness, rolling of tongue, epigastric pain	100 mg 8th hourly	Intravenously	3	50 mg 12th hourly	Intravenously	3	Seizures, Slurred Speech, Twitching of Muscles, Ataxia, Nystagmus	Nil	Positive
2	Seizures, Right shoulder pain	200 mg at bed time,	Oral (Tablet)	14	150 mg 12th hourly	Oral (Tablet)	14	Sever Shoulder pain followed by an episode of Seizure, Hypotension (BP 90/60 mmHg)	Paediatric	Positive

3	Seizures	400 mg in 250 ml of Normal Saline (NS) infusion for 1 hour	Intravenously	3	50 mg 12th hourly	Intravenously	3	Abdominal pain, vomiting, Headache, Seizure, Disorientation	CKD & Metronidazole	Positive
4	Drooling of saliva, tongue bite	400 mg in 100 ml NS, 100mg BID	Intravenously Oral (Tablet)	1 2	150 mg 12th hourly	Oral (Tablet)	5	seizure episode involving Right upper limb with prodromal symptoms and loss of consciousness Giddiness and confusion	Sodium Valproate	Positive
5	Seizures, semiconscious, hematemesis, BP: 130/90 mm of Hg	400 mg in 100 ml NS 100mg HS	Intravenously Oral (Tablet)	1 1	50 mg 12th hourly	IV	2 days	Seizure, Hypotension, BP: 80/60mm Hg	NIL	Positive

[**BP-Blood pressure, *NS-Normal saline, * HS-hours of sleep, *BID-Bis in die, *IV-Intravenous]

Table 3: Patient Treatment and outcome

Patient	Treatment	Phenytoin Cessation	Time for Improvement
1	Midazolam	Yes	After 4 days
2	Midazolam	Yes	After 2 days
3	Sodium Valproate	Yes	After 2 days
4	Carbamazepine	Shifted Infusion to oral and then stopped after 2 days	After 2 days
5	Diazepam and IV fluids	Yes	After 3 days