www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i4.34

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Case Study

Drug – Drug Interaction of Phenytoin and Isoniazid

Authors
Dr Sonali Ramakant More[1], Dr Balasaheb Baburao Ghongane[2]
Dr Bharti Ramchand Daswani[3]
[1]Assistant Professor, [2]Professor and Head, [3]Associate Professor
Department of Pharmacology, B.J. Government Medical College and Sassoon General Hospital
Pune – 411001 Maharashtra, India
Corresponding Author
Dr Sonali Ramakant More*
Email- *sonamore11@gmail.com* M- +91:9619677292

ABSTRACT
Phenytoin is a first line anti-epileptic drug; however side effects and drug interactions are seen with it frequently as it is a narrow therapeutic indexed antiepileptic drug. Many drugs competitively inhibit iso-enzymes responsible for its metabolism when concurrently administered and increases the phenytoin plasma concentration leading to serious adverse effects. One such case is being reported with phenytoin toxicity due to concurrent administration of phenytoin and isoniazid. It reflects the possibility of potential drug-drug interactions, as well as aims to highlight the importance of spontaneous reporting of adverse drug reactions amongst prescribing physicians and therapeutic drug monitoring in case of drugs with low safety margin.
Keywords-*Drug Interaction, Phenytoin toxicity, Isoniazid, therapeutic drug monitoring.*

Introduction

Phenytoin is one of the most commonly used antiepileptic medications in clinical practice for generalized seizures. It acts by slowing the rate of recovery of voltage-activated sodium channels from inactivation. Phenytoin is metabolized by CYP2C9/10 and CYP2C19. Because its metabolism is saturable, other drugs that are metabolized by these enzymes can inhibit the metabolism of Phenytoin and increase its plasma concentration. [1,2] It is known to cause a range of deleterious and erratic side effects including nystagmus, ataxia, facial puffiness, urinary incontinence, enlargement of lips, hepatitis, rash and vomiting. Acute oral over dosage results primarily in signs referable to the cerebellum and vestibular system. Toxic effects with chronic treatment also are primarily dose related cerebellar-vestibular effects, but also include behavioural changes, seizures, GI symptoms, gingival hyperplasia, hirsutism, osteomalacia, and megaloblastic anaemia. Control of seizures is generally obtained at total concentrations above 10 microgram/ml, while toxic effects like nystagmus develop at total concentrations around 20 microgram/ml [2,3,4] Drug interactions may alter phenytoin concentrations in plasma and become clinically very significant due to its narrow therapeutic index. The risk of Phenytoin toxicity

increases among the patients concurrently receiving Isoniazid, due to impaired phenytoin metabolism by Isoniazid with an increased incidence up to 19% [5]

Case Report

A 29 year old male patient belonging to the lower socio-economic status presented to the neurology outpatient department (OPD) on 22.2.2017 with complaints of decreased urine output, enlargement of lips, facial puffiness, vomiting, generalized body rashes, blurring of vision and unsteadiness of gait since 2 days.

On examination; patient was conscious, oriented, with pupils bilaterally equal. His tendon reflexes were normal and power was Grade 4 on left side, Grade 5 on right. However, he showed positive signs of nystagmus and ataxia, and his finger-nose co-ordination was impaired.

He was diagnosed with generalized tonic clinics seizures since 2 years i.e from February 2015. He had received Tablet Phenytoin 100 mg three times a day half an hour before food. His past medical history revealed that he was diagnosed with tubercular meningitis 2 months back (December 2016) for which he was hospitalised and on anti-tubercular drugs since then (Isoniazid 300 mg, Rifampicin 600 mg, Pyrazinamide 1500 mg, Ethambutol 800 mg once daily 2 hours after daytime meal). There was no family history of generalised tonic clonic seizure and tubercular meningitis. There was no any medication consumption history other than phenytoin and anti – tubercular drugs since last 10 years of his life.

After 2 months from beginning of treatment of tubercular meningitis, the patient presented to the neurology department with complaints of blurring of vision, difficulty in walking, unsteadiness, generalized macular rashes over limbs, chest and back, vomiting, urinary incontinence and decreased urinary output. He was admitted to the in-patient medicine ward on 22 February 2017. This episode was occurred early in the morning after he woke up. Patient was unable to get up from bed; hence he was admitted on the same day. Last dose of phenytoin was taken in the previous night, half an hour before meal likewise last doses of anti – tubercular medications were consumed on the previous day of episode 2 hours after daytime meal. His blood sample was sent to the Department of Pharmacology for Serum Phenytoin estimation to rule out toxicity on the next day of admission. MRI scan of the brain and spinal cord did not reveal any organic/structural lesions. USG of abdomen including the KUB region was normal. Liver function tests showed a fourfold elevation in amino transferase levels (SGPT- 150mg/dl and SGPT-96mg/di). His other investigations revealed Total Bilirubin 0.8 mg/dl, Total Protein 8.3 g/dl, Total Albumin 4.21 g/dl, Total Globulin 3.88 g/dl and Serum Creatinine 0.69 mg/dl, all of which fall within normal limits.

A provisional diagnosis was made of phenytoin toxicity. Based on the clinical findings and other evidences, phenytoin and all anti-tubercular medications were de-challenged and the patient was started on Tablet Levetiracetam 500 mg per day and Tablet Carbamazepine CR (200 mg) per day for epilepsy, Ondansetron 4 mg for vomiting, Fusidic acid cream for rash, Ursodeoxycholic acid 300 mg for hepatitis.

Phenytoin assay showed that his serum Phenytoin levels were found to be > 40 mcg/ml (reference range: 15-20 mcg/ml). His Serum Phenytoin levels came out to be 43.76 micrograms/ml on estimation (ClinRep kit for detection of Antiepileptics in serum by HPLC, Hitachi UV Detector L-2400 Wavelength 205 nm, Flow rate 1ml/min, Agilent EZChrom Elite Software edition 2006). Ophthalmological examination revealed gaze included horizontal nystagmus.

After 2 weeks of hospitalization and withdrawal of Phenytoin and ATT, the patient showed a dramatic improvement in symptoms including the visual blurring episode, ataxia, vomiting, enlargement of lips, urinary incontinence and rash. His signs of nystagmus and ataxia resolved gradually over a span of 5 days, following which he was discharged on 9.03.2017. Aminotransferase levels were also found normal in subsequent liver function tests. (SGPT- 45mg/dl and SGOT- 35mg/dl) He was advised to continue Tablet Levetiracetam 500 mg

per day and Tablet Carbamazepine CR (200 mg) per day for epilepsy as well as continue same medications for tubercular meningitis with follow up at the neurology OPD after 15 days as there could be chances of drug - drug interaction of carbamazepine and isoniazid. Hence follow up is critical for this patient.

Discussion

Phenytoin is one of the most widely-prescribed antiepileptic drugs in clinical practice for the management of generalised tonic clonic seizures and complex partial seizures. It may also be used in the prevention of seizures following head trauma, and in ventricular arrhythmias. The absorption of phenytoin varies with dosage form and in the salt form absorption is rapid and more than 90%. It is highly protein bound and extensively metabolised by hepatic microsomal isoenzymes CYP2C9 and CYP2C19 [6]. Phenytoin follows zero order kinetics at therapeutic concentrations, because the rate of metabolism is close to the maximum capacity of the enzyme involved. Clinically effective serum level is usually 10–20 mcg/mL. With recommended dosage, a period of seven to ten days is adequate to achieve steady-state plasma concentration of phenytoin [7]. When phenytoin is co-administered with Isoniazid, the serum concentration levels of phenytoin will significantly increase due to competitive inhibition of CYP2C19 by Isoniazid. A report from previous study suggests that consequences of drug interaction are manifested between 5-22 days [5].

In this patient, phenytoin toxicity was observed after 11 weeks. Investigations were carried out to exclude any structural organic cause for the clinical manifestations and found all negative. His blood laboratory parameters were within normal limits, ruling out any derangements in liver and kidney functions resulting in modification of Phenytoin therapy. The symptoms experienced by the patient in question are understandable in terms of complex pharmacokinetics, narrow therapeutic index and individual variability in metabolism and elimination of phenytoin. This patient developed exaggerated side effects gradually over a period of 3 months after the concomitant use of phenytoin with Isoniazid, which can be explained by gradual elevation of the drug in the plasma over the time as the pharmacokinetic of the phenytoin follows ranging from 1st order kinetic to Zero order kinetic, hence even minor dosage changes can result in variable concentration as the elimination is saturated. Follow up for this patient is critical because there could be possibility of drug - drug interaction of carbamazepine and isoniazid. It is a potent enzyme inducer, and after about two weeks dosing auto induction occurs, the mean half-life falls from 30 to 18 hours, and the serum concentration may fall. Isoniazid is a potent hepatic enzyme inhibitor. It is acetylated in the liver at a rate that varies between individuals and shows a bimodal distribution in the population, with slow and rapid acetylators. Slow acetylators could have a much greater risk of experiencing the interaction between isoniazid and carbamazepine [8]. Hence, plasma level monitoring of carbamazepine is too essential in such cases.

It also highlights the importance of Therapeutic drug monitoring, especially in patients receiving low safety margin drugs like anticonvulsants. Measurement of plasma concentration can give an estimate of the pharmacokinetic variables in that patient so that appropriate adjustments in the dosage can be made and adverse events avoided [9]. Drug-drug interactions are said to account for 6%- 30% of all adverse events, and they continue to pose significant risk to patient's health outcomes and a considerable burden on the health care system [10]. It is therefore, the need of the hour to sensitize the prescribers about the same especially regarding the importance of eliciting a complete drug history before writing a prescription. Ensuring co-ordination in prescribing between the different treating physicians, as in this case the Chest TB OPD and Medicine OPD, would also go a long way in preventing Adverse Drug Reactions as would spontaneous reporting, and documenting of anypossible, probable or definite adverse reactions that one comes across.

Conclusion

This case report serves as an alert to clinicians to remain clinically vigilant for such manifestations in patients when phenytoin and Isoniazid are concomitantly administered. While prescribing Isoniazid and phenytoin, a caution on dosage adjustment of phenytoin is advisable. Since specific guidelines for adjustment of dosage are not established, it is recommended that the required dosage of phenytoin in such situations be guided by the clinical symptoms as well as frequent neurological evaluation serum assay of phenytoin whenever indicated.

References

1. Livanainen M, Savolainen H. Side effects of phenobarbitol and phenytoin during long term treatment of epilepsy. Acta Neurol ScandSuppl 1983; 97:49-67.
2. Brunton L, Chabner B, Knollman B. Goodman and Gillmans Pharmacological Basis of Therapeutics. 12th Edition. Mc Graw Hill, USA. 2011. Chapter 21, Pharmacotherapy of the Epilepsies; p591-593.
3. Larsen JR, Larsen LS. Clinical features and management of poisoning due to phenytoin. Med Toxicol Adverse Drug Exp 1989;4 (4):229-45.
4. Roger L. Nation. Pharmacokinetic Drug Interaction with Phenytoin (part 1). Clin.Pharmacokinet. 18 (1):37-60,1990.
5. Russell R. Miller, J Porter, D J Greenblatt. Clinical importance of Interaction of Phenytoin and Isoniazid: A report from the Boston collaborative drug Survillance Program. CHEST 1979;75(3):356-358.
6. ZeruesenayDesta, Nadia V Soukhova, David A Flockhart. Inhibition of cytochrome P450 (Cyp450) isoforms by Isoniazid: potent inhibition of Cyp2C19 & Cyp3A. Antimicrob agents Chemother. 2001; 45(2): 382-392.
7. Hussein A, Abdulgalil A, Omer F, Eltoum H, Hamad A, El-Adil O, et al. correlation between serum level of antiepileptic drugs and their Side Effects. Oman Med J 2010; 25(1): 17-21.
8. James M. Wright, Elaine F. Stokes, Vincent P. Sweeney. N Engl J Med 1982; 307:1325-1327.
9. K.D Tripathi. Essentials of Medical Pharmacology. 7th Edition. 2013. Chapter 3, Pharmacokinetics: Metabolism and Excretion of Drugs, Kinetics of Elimination; p33-34.
10. Soherwardi S, Chogtu B. Surveillance of the Potential Drug-Drug Interactions in the Medicine Department of a Tertiary Care Hospital. Journal of Clinical and Diagnostic Research. 2012 September (Suppl), Vol-6(7):1258-1261.