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Research Article

A case of Phenytoin toxicity

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Abstract

Phenytoin is a first line anti epileptic agent; however side effects and drug interactions are seen with it frequently. We hereby report a case of Phenytoin toxicity, evidenced by elevated plasma concentration of the drug, along with cerebellar and vestibular manifestations in a patient receiving an array of other concomitant medications. It reflects the possibility of potential drug-drug interactions, as well as aims to highlight the importance of spontaneous reporting of adverse drug reactions among prescribing physicians and therapeutic drug monitoring in case of drugs with low safety margin.

Key-words: Phenytoin toxicity, drug interaction, therapeutic drug monitoring.

Introduction

Phenytoin is an anti epileptic drug that 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.

Acute oral overdosage 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.[1]

Case History:

A 33 year old female presented to Medicine OPD on 17.06.2013, with complaint of giddiness and headache since 8 days. She had no history of blurring of vision, ear discharge, vomiting, or head trauma.

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

On enquiry, she was found to be receiving Tab Phenytoin (*Eptoin)* 100 mg twice daily, since 2006 when she presented with left sided hemiplegia and was diagnosed having cerebral venous sinus thrombosis.

She was also receiving Folate supplements for the past 6 years. On scrutinizing her previous prescription records, it was found that she had additionally been on Tab Enalapril 2.5 mg OD and Tab Acetyl Salicylic Acid (ASA) 150 mg OD, regularly since 4 years.

She was found to be seropositive for HIV in October 2012, for which she had received Tab Zidovudine 300 mg, Tab Lamivudine 150 mg, Tab Nevirapine 200 mg for initial 3 months; being later switched to the regimen containing Tab Lamivudine 150 mg, Tab Nevirapine 200 mg, Tab Tenofovir 500 mg which continued till date.

She was admitted to the in-patient ward, her blood sample was sent to the Department of Pharmacology for Serum Phenytoin estimation to rule out toxicity.

She was also advised CT brain to rule out cerebellar bleed.

On the same day, she was given Inj Mannitol 100 cc stat and started on Tab Warfarin 5mg OD, Tab Amlodipine 100 mg BD, Tab Atenolol 50 mg OD and Tab Carbamazepine 200 mg OD.

Tab Eptoin 100 mg BD, Tab Enalapril 2.5 mg OD and Folate supplementation was continued.

Her Serum Phenytoin levels came out to be 40.53 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). CT report suggested an ill defined non enhancing hypodense lesion on the sub cortical white matter in the right temporo-parietal region suggestive of oedema. Her other investigations revealed Total Bilirubin 0.8 mg/dl**,** Total Protein 8.2 g/dl**,** Total Albumin 4.3 g/dl**,** Total Globulin 3.86 g/dl and Serum Creatinine 0.7 mg/dl, all of which fall within normal limits.

Since Phenytoin toxicity was suspected, Tab Eptoin and Tab Warfarin were stopped and rest continued.

Her signs of nystagmus and ataxia resolved gradually over a span of 5 days, following which she was discharged on 23.06.2013. She was advised to continue Tab Carbamazepine CR (200 mg) daily, and follow up at the OPD after 15 days, for which she did not return.

Discussion

In this case, patient had been clinically well controlled on *Eptoin* without any adverse drug reactions for 6 years but had recently developed signs of Phenytoin toxicity. Her blood laboratory parameters were within normal limits, ruling out any derangements in liver and kidney functions resulting in modification of Phenytoin therapy.

Considering the potential for drug interactions with Phenytoin, it was realised that she had been simultaneously receiving several other drugs like Folate supplements along past 6 years; Enalapril and ASA since past 4 years; Zidovudine, Lamivudine, Nevirapine for 3 months since October 2012; and was later switched to Lamivudine, Nevirapine, Tenofovir since past 6 months. A literature search failed to document evidence of any interaction between Enalapril and Phenytoin, ASA has been shown to displace Phenytoin from its protein binding sites and may lead to an increase in free drug concentration in the plasma.[2] However, she had been stable on this regimen for many years and signs of Phenytoin toxicity developed only recently. Hence, interaction of Phenytoin with these drugs as a cause of current symptoms is unlikely, as in this situation manifestations would have appeared earlier.

Considering the fact that current manifestations of Phenytoin toxicity appeared in less than a year of starting ART, we searched for literature on potential drug interactions between Phenytoin and ART. Reports suggest that co administration of Zidovudine or Lamivudine with Phenytoin may lead to complex drug interaction, resulting in an increase or decrease in plasma Phenytoin concentration.[3,4]

Phenytoin is known to affect hepatic /intestinal of CYP3A4 and may thus decrease the serum levels of Nevirapine. Both may compete for protein binding**,** and resulting in anticonvulsant toxicity.[5]

Again, Zidovudine had been replaced by Tenofovir in her ART regimen, and Lamivudine and Nevirapine have been part of her treatment regimen for long, as compared to Tenofovir which was a relatively recent addition.

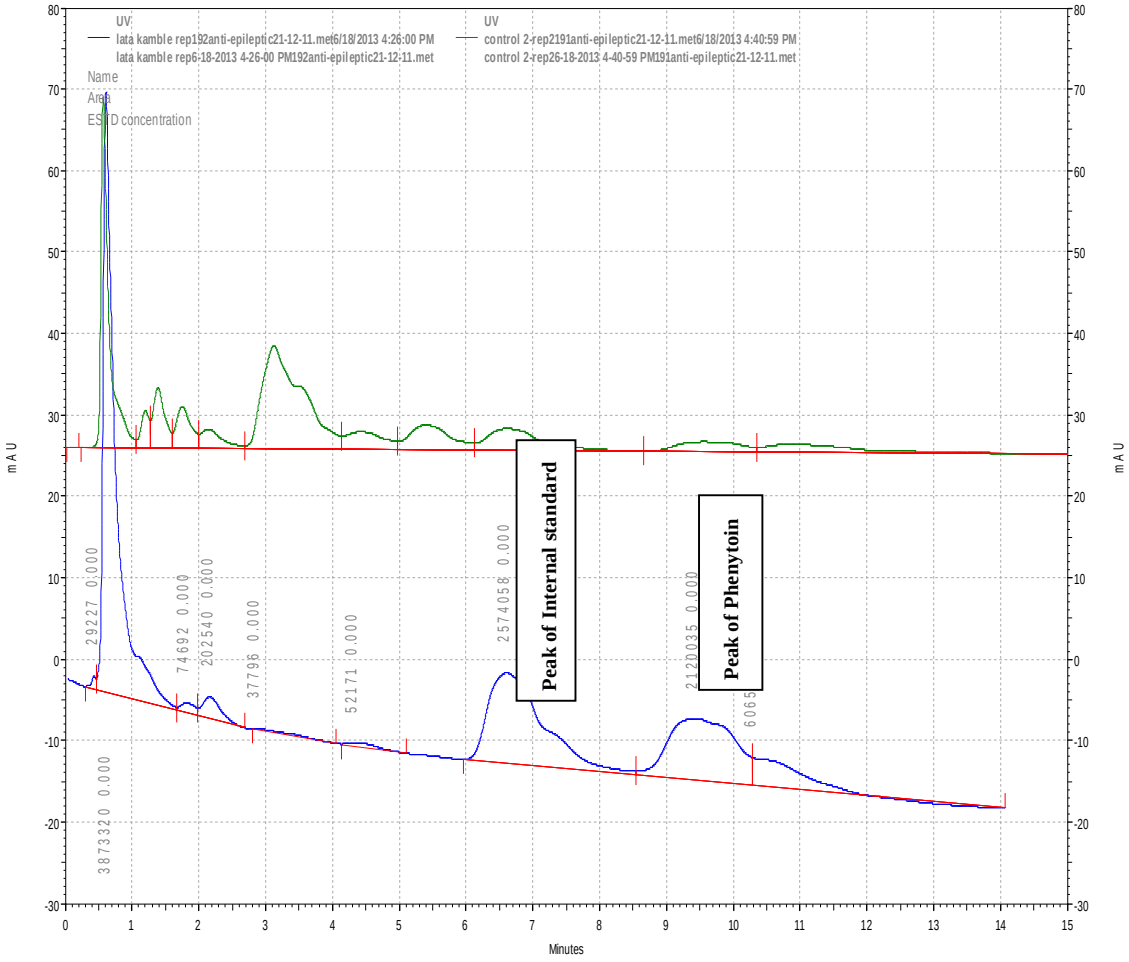
Although documentation of interaction between Tenofovir and Phenytoin is scarce,[6] interaction between the two cannot be completely ruled out as the above case suggests such probability.

Whether the potential sub-threshold interaction between Phenytoin, Nevirapine and Lamivudine had been precipitated by addition of Tenofovir also needs a mention as it highlights the increase in risk of clinically manifest Drug-Drug interactions as number of drugs in the prescribed regimen increase.

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.[7]

Drug-drug interactions are said to account for 6%-30% of all adverse events, and they continue to pose a significant risk to patient's health outcomes and a considerable burden on the health care system.[8]

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 ART OPD and Medicine OPD, would also go a long way in preventing Adverse Drug Reactions. As would spontaneous reporting, and documenting of any possible, probable or definite adverse reactions that one comes across.



Chromatogram of Control solution and Patient's sample

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