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LETTER TO THE EDITOR

Phenytoin-Induced Toxicity Due To Drug Interactions

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ABSTRACT

Phenytoin is effective against both partial and tonic-clonic seizures. It is said to act by limiting repetitive firing of action potentials evoked by sustained depolarization, mediated by slowing the rate of recovery of voltage activated sodium channels from inactivation.The optimal initial dose, suggested for phenytoin is 3 to 4 mg/kg, body weight /day, while the usual maintenance dose is 200 to 500 mg/day for an adult. Phenytion is completely absorbed from upper intestine and is metabolized by liver. It undergoes entero-hepatic recycling and is excreted in urine, either as free or conjugated form. It is widely distributed throughout the body and is extensively plasma protein bound (90%). The toxic effects of phenytoin depend upon the route of administration, duration of exposure and dosage. Its toxic manifestations present as a syndrome comprising of cerebellar, vestibular and ocular effects such as nystagmus, diplopia, slurred speech and ataxia. Mental confusion and exacerbation of seizure frequency have also been noted. Overdose leads to hypotension, coma and respiratory depression. The dosage adjustments of phenytoin are necessary, to achieve adequate control of seizures, along with monitoring of its plasma concentration. This is because it follows saturation kinetics such as the rate of elimination varies as a function of its concentration. The plasma half-life ranges from 6 to 24 hrs at plasma concentration below 10 μg/ml, but increases with higher concentration. As a result, even with small increments in it's dosage to attain the levels towards therapeutic range, plasma drug concentration may increase disproportionately leading to toxicity. While, several reports are available indicating adverse drug reactions to phenytoin, the following case illustrates how phenytoin toxicity is affected by its interaction with other drugs especially in situations of polypharmacy.

Case report

A 50-year-old woman was brought with a history of diabetes of 2 yrs duration, treated with insulin. She was also reported to be on antihypertensive medication, atenolol 50 mg, once daily, for 17 yrs and aspirin 75 mg, once daily for prophylaxis of myocardial infraction.

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Patient gave history of periodic consumption of ibuprofen 200 mg and combination of calcium carbonate and vitamin D_3 (shelcal) 500mg, for her osteoarthritis of 20 yrs duration.

The patient was admitted with a provisional diagnosis of chronic renal failure as a result of non-steroidal anti-inflammatory drugs (NSAID) abuse, along with seizure disorder. Diagnosis of myoclonic jerks secondary to metabolic factors was made and she was advised additional treatment with phenytoin 100 mg, thrice daily along with clonazepam 0.5 mg,

once daily. As the patient had symptoms of peptic ulcer she was prescribed pantoprazole 40 mg, once daily. Patient was subsequently discharged a week later with a note to continue the above medications and was asked to come for a follow-up visit to the out-patient department after 15 days.

However, the patient developed symptomsof inability to coordinate voluntary movements and excessive weakness ten days after starting phenytoin for metabolic seizures along with pantoprazole for peptic ulcer. However patient sought admission two days later. A diagnosis of ataxia, secondary to phenytoin toxicity was then made. Her hemoglobin was 10.2 g/dl and HBsAg was negative. Serum sodium 128mEq/L, potassium 3.9 mEq/L and chloride 97 mEq/L. Fasting blood sugar was 159 mg/dl and her serum phenytoin level was > 40 μg/ml (normal range = 10-20μg/ml) at the time of admission and 30 > μg/ml, two days after the admission.

On the day of admission, the patient was treated with amlodipine 2.5 mg, once daily and combined vitamin B_1, B_6 and B_{12} (Neurobion) 5000 units, intramuscularly. She also received hepatitis B (Shanvac) 1 ml IM and oral salt 5-6 gm/day, in addition to the previous treatment regimen for diabetes, hypertension and peptic ulcer. Hepatitis B vaccine was found to have been given as a part of protocol defined for the treatment of chronic kidney disease to prevent hepatitis infection during the course of dialysis and oral salt to compensate for low sodium level i.e. 125 mEq/L (135-145 mEq/L). Since her serum phenytoin level was high, the drug was withheld for one day and she was prescribed clonazepam 2mg intravenously as needed, if she had a seizure. After a 24-hr break her blood sample was sent for estimation of phenytoin levels and was restarted on 100 mg of phenytoin once a day, along with clonazepam 0.5 mg once daily. During her stay in the hospital ataxia was reported to be less severe and her phenytoin level was 30 μg/ml two days after the admission.

Discussion

In this patient, ataxia was identified to be secondary to phenytoin toxicity, as a result of pharmacokinetic drug interactions which may be due to multiple medications she received.

Pantoprazole an anti-peptic ulcer agent, inhibits oxidative hepatic metabolism of phenytoin[2], decreases it's plasma clearance by 15% and increases it's elimination half life by 27%, resulting in higher serum levels. Ibuprofen is an anti-inflammatory drug and when co-administered with phenytoin is known to inhibit hepatic metabolism of phenytoin and also displace phenytoin from albumin binding sites [3], which may increase the levels of phenytoin. Amlodipine is a calcium channel blocker and phenytoin when co-administered is known to induce the cytochrome P450 3A4 system and is reported to reduce bioavailability of calcium channel blockers [4]. Salicylates can also affect the serum levels of phenytoin by increasing the plasma-free phenytoin fraction [5]. Further, there is evidence for phenytoin-induced hyperglycemia and hypocalcemia, which deserves a careful consideration of using these drugs along with phenytoin, as she is a known diabetic. Also, the decrease in serum calcium concentration to hypocalcemic values, along with significant reduction in 25 hyroxy-cholecalciferol concentration and increase in alkaline phosphatase, by phenytoin may worsen osteoarthritis [1].

Suggestions for safer medications

In the present patient, a H2 (histamine) receptor blocking agent can be substituted to treat peptic ulcer in place of pantoprazole. The NSAIDS such as aspirin and ibuprofen may be avoided or given as and when required because they have a tendency to produce gastrointestinal damage, bleeding and interactions altering blood phenytoin levels. . As the patient was already receiving atenolol for blood pressure control, the use of a calcium channel blocker should be reassessed.

Conclusions

Thus, the increased serum levels of phenytoin in this patient appear to be due to drug-drug interactions and clinicians should pay special attention to the usage of drugs such as pantoprazole, NSAIDs and Calcium channel blockers when a patient is receiving phenytoin for seizure disorder.

Conflict of Interest: None declared

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