Drug Interaction Between Phenytoin And Oxacarbazepine: A Case Report On Phenytoin Toxicity

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Background: Phenytoin is a commonly used anti-epileptic or anticonvulsant drug. It is mainly used to treat tonic clonic seizures as well as complex partial seizures. Due to the use of drug in overdose, medication errors, drug interactions with other anticonvulsant drugs in multiple dosage regimen causes some serious toxicities includes osteomalacia, teratogenicity, lymphadenopathy, gingival hyperplasia, ataxia, diplopia, nystagmus.

Case: A 24 years old female patient presented with complaints of diplopia, giddiness, nystagmus, general weakness and nausea while she was using phenytoin of dose 200mg twice daily with combination of clobazam since 2months to treat partial seizures. She had medical history of suffering from partial seizures in the last 10 years on medication with oxacarbazepine of dose 150mg at morning, 450mg at night time daily. while using this medication, she got a fever then physician prescribed paracetamol of dose 650mg twice daily and advised to stop oxacarbazepine and prescribed phenytoin of dose 200mg with clobazam of dose 10mg.Due to the lack of medication adherence she used to take phenytoin with clobazam and oxacarbazepine at one time daily, after using this medication for 2months ,the levels of phenytoin in blood increases causes severe toxicities. Then physician advised to stop phenytoin intake and prescribed carbamazepine.

Keywords: Osteomalacia, Nystagmus, Diplopia, Oxacarbazepine, Clobazam.
INTRODUCTION:
Phenytoin /5-5diphenylhydantoin (DPH) is widely prescribed first line drug for simple, complex partial seizures and mainly used for tonic clonic seizures [1,2] except myoclonic (absence seizures)[1,2].95% of drug is bound to plasma proteins (mostly albumins). It is mainly metabolized by hepatic P450 enzyme CYP2C9(90%) and CYP2C19(10%). Phenytoin have narrow therapeutic range of 10-20mcg/ml [1,4]. Protein bound phenytoin does not cross blood brain barrier but free phenytoin (unbound) in blood cross blood brain barrier causes encephalopathy.

Oxcarbazepine is structural derivative of carbamazepine mainly used to treat partial seizures. When we take the oxcarbazepine with phenytoin, the concentration of phenytoin in the blood increases and levels of oxcarbazepine reduces make the medication less effective [3,4]. Research studies suggest that levels of phenytoin in the blood increases with oxcarbazepine and carbamazepine, these drugs inhibits the phenytoin metabolism using human liver microsomes and cDNA-expressed CYP2C19 [4,5]. These drugs inhibits CYP2C19-mediated phenytoin metabolism at therapeutic concentrations[4].

The following are the phenytoin plasma concentrations and there possible side effects obtained in most of research studies[3].

- Less than 10mcg/ml: no side effects or rare
- 10 -20mcg/ml: occasional mild horizontal nystagmus on lateral gaze
- 20-30mcg/ml: Nystagmus
- 30-40mcg/ml: Taxia, slurred speech, tremor, nausea and vomiting
- 40-50 mcg/ml: Lethargy, confusion, hyperactivity
- Greater than 50mcg/ml: Coma and seizures

CASE REPORT
A 24 years old female patient presented with the chief complaints of diplopia, giddiness, nystagmus, general weakness and nausea. On examination patient was conscious and coherent. Blood pressure was found to be 90/60mmhg (hypotension). Her pulse rate was found to be 83 beats per minutes, respiratory rate was normal.

She had a history of epilepsy (partial seizures) since 10 years on medication with oxcarbazepine of dose 150mg at morning ,450mg at night time daily and her father had hypertension and occasional seizures on medication with carbamazepine. While she was using this medications for seizures, she got a fever then physician advised to stop oxacarbazepine and prescribed paracetamol of dose 650mg twice daily and phenytoin of dose 200mg twice daily with clobazam of dose 10mg. Due to lack of better medication adherence, she used to take phenytoin at morning time with clobazam and oxacarbazepine 450mg at night time, sometimes she used to take all three phenytoin, clobazam and oxacarbazapine at a time twice daily for 2 months. Then drug interaction between phenytoin and oxacarbazepine, increases the concentrations of phenytoin in blood and shows the toxic symptoms in the patient made her hospitalized condition.

After admitted into the hospital with severe toxicities of phenytoin, serum phenytoin levels was found to be more than 40mcg/ml(normal range: 15-20mcg/ml). Hematology report was found be hemoglobin 9grams/dl, WBC count 10800cmm, RBC count 5.5million/cm, Neutrophils 76%, Lymphocytes 21%, Eosinophil 1%, Monocytes 02%. Serum electrolytes are found be sodium 137mmol/L, potassium 4.3mmol/L, chlorine 1.4mmol/L and serum creatinine found be 0.6mg/dl, Blood urea 13mg/dl and Random blood sugar is found to be 99mg/dl.

TREATMENT
Physician was advised to stop phenytoin with clobazam and prescribed tablet carbamazepine of dose 200mg twice daily and tablet betahistine dichloride of dose 16mg once daily at bed time and injection ondansetron 4mg intravenous administration and intravenous fluids to increase the blood volume. After using this medication for 15 days with the withdrawal of phenytoin, her symptoms got normal and there no reoccurrence of seizures.

DISCUSSION
Phenytoin and oxacarbazepine are the first line drugs commonly used to manage the epilepsy condition
Phenytoin have narrow therapeutic range 10-20mcg/ml[1,3], phenytoin attains the saturated state at higher dose administration and elimination follows zero order. Commonly half life of phenytoin is 6-24 hours but increases gradually with higher concentrations in plasma [1,2,5]. At higher concentrations of phenytoin in plasma leads to zero order elimination results in increase the duration of half life[1]. Due increased duration of half life in drug results in prolonged duration of toxic symptoms. Oxacarbazepine as a similar mechanism of action of carbamazepine but this is less susceptible to hepatic enzyme metabolism. This is more potent than carbamazepine and due to less involvement in hepatic enzyme metabolism shows the lesser sideeffects, interactions. The half life of oxacarbazepine is 1-2 hours, elimination follows first order. As per studies oxacarbazepine of dose 1200mg/day with combination of phenytoin leads to severe toxicities. Has the concentration of oxacarbazepine increases in plasma its inhibits the CYP2C19 mediated phenytoin metabolism results in increase in phenytoin plasma concentration leads to the saturated state that follows the zero order elimination but oxacarbazepine only effect the 10% of phenytoin metabolism, to increases the concentration of phenytoin in plasma >20mcg/ml it takes several days. Phenytoin reduces the efficacy of oxacarbazepine and levels of oxacarbamazepine in plasma gradually decreases[3,4].

CONCLUSION
Phenytoin with other antiepileptic drugs shows mild to moderate drug interactions. Phenytoin with oxacarbazepine is moderate drug interaction but if dose of oxacarbazepine exceeds 1200mg per day with phenytoin leads to severe toxicities, dose adjustments is needed and monitor phenytoin plasma concentration if any toxic symptoms developed while using the medication. If there are severe toxic symptoms of phenytoin can increase the patient quality of life.

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REFERENCE