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Case Report

Diverse presentations of phenytoin toxicity-presenile cataract, encephalopathy and peripheral neuropathy: a case series

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ABSTRACT

One of the most commonly used antiepileptic drugs, phenytoin, has a narrow therapeutic index, high plasma protein binding, non-linear pharmacokinetics and inter-individual variability. It can also present with adverse drug reactions due to phenytoin toxicity with diverse presentations mimicking symptoms of other diseases thus causing diagnostic predicament. This case series reports three such cases of uncommon presentation of phenytoin toxicity like presenile cataract, fluctuating encephalopathy with diurnal variation and peripheral neuropathy. Monitoring of serum drug levels in such cases aids in confirming drug toxicity. Adverse drug reaction monitoring helps in early detection and appropriate management of drug related morbidity.

Keywords: Phenytoin, Adverse drug reaction, Therapeutic drug monitoring

INTRODUCTION

Phenytoin is one of the most commonly prescribed antiepileptic drug, however it is very difficult to adjust its dose. Since it has a narrow therapeutic index, high plasma protein binding, non linear pharmacokinetics and interindividual variability, it commonly causes dose-related toxicity.[1] Phenytoin toxicity may have variable presentations. Some dose-related adverse effects may be similar to symptoms of other diseases. In such cases serum drug levels help in confirming phenytoin toxicity.[1]

The purpose of this case series is to highlight the diverse and uncommon presentations of phenytoin toxicity presenting as symptoms of other disease causing a diagnostic dilemma.

Presenting here are three interesting cases of phenytoin toxicity who were admitted as case of presenile cataract, fluctuating encephalopathy with diurnal variation and peripheral neuropathy. Written informed consent has been taken from each patient.

CASE REPORT

Case 1: Bilateral presenile cataract due to phenytoin toxicity

A 20 year old male presented with painless progressive decrease in vision in both eyes (right > left) since past two years. He was a known case of epilepsy since past three years and was on treatment with phenytoin 100 mg twice daily. Slit lamp examination revealed bilateral diffuse posterior subcapsular cataract (cortical). Detailed investigations to find out the cause of such presenile cataract were normal. However serum phenytoin levels done was 47 mcg/ml (high). Hence in the absence of other causes, the cataract was attributed to phenytoin toxicity. The patient underwent bilateral cataract surgery with posterior chamber intraocular lens implantation, two

months apart, with a good post-operative vision of 6/6 in both eyes. Also his antiepileptic drug was changed from phenytoin to levetiracetam 500 mg thrice daily.

Case 2: Fluctuating encephalopathy with diurnal variation due to phenytoin toxicity

An 85 year old man presented with history of episodic unconsciousness lasting few hours daily since past 15 days. Patient would not wake up in the morning (which he used to do by 6am earlier) and would be unresponsive to call or vigorous shaking, till about 10 am when he would be initially drowsy for 1-2 hours and later be alert for the rest of the day. This duration of unresponsiveness kept on increasing everyday till it reached afternoon time. He also complained of mild giddiness during the day. There was past history of intracerebral haemorrhage 2 years back for which he was given prophylactic anticonvulsant (oral phenytoin 100 mg thrice daily). Examination in awake state revealed nystagmus and ataxia. Phenytoin toxicity was suspected and serum phenytoin levels done subsequently were high (46.48 mcg/ml). Other investigations done were normal. Phenytoin was therefore stopped and within 2 days his ataxia improved and 5 days later his sleep pattern was back to normal and there was no diurnal unresponsiveness.

Case 3: Peripheral neuropathy due to phenytoin toxicity

A 58 year old man presented with generalised tonic clonic status epilepticus, and was treated with injection lorazepam and phenytoin (loading and maintenance). He was discharged on oral phenytoin 100 mg thrice daily. 15 days after discharge patient developed a morbilliform rash on extremities and trunk. However patient presented to hospital 4 months later with history of gait ataxia, diplopia, difficulty in getting up from squatting position and paresthesias in lower limbs. Examination revealed bilateral nystagmus, hand tremor, severe gait ataxia, weakness and distal sensory loss in both lower limbs. Nerve conduction studies showed evidence of axon loss symmetric distal sensory motor neuropathy. Serum phenytoin level done was 48 mcg/ml. Since all other investigations were normal, the above findings were attributed to phenytoin. It was replaced with levetiracetam. Few days later the patients ataxia improved, rash started subsiding and in a few months' time, paresthesias and weakness decreased.

DISCUSSION

Phenytoin is a commonly prescribed antiepileptic drug which is effective in all types of partial and tonic clonic seizures except absence seizures.

Phenytoin is available in oral and injectable formulation. The oral forms of phenytoin are capsule, tablet, suspension. Oral formulation can be in rapid release form given as BD or TDS or extended release form given once daily. Formulations can include either phenytoin base or phenytoin sodium salt. Phenytoin base is available as suspension, chewable tablets while phenytoin sodium is available as tablets, capsules and injections. 100 mg of phenytoin sodium=90 mg of phenytoin base.[2] This necessitates dosage adjustments and serum phenytoin level monitoring as per phenytoin equivalents when switching between salt and base and also different market preparations (bioavailability of same strength/form but different brands, may differ).[3] Injectable phenytoin sodium is mostly given intravenously as slow injection or infusion at a rate of 50 mg/minute in adults and 1-3 mg/kg/minute (or 50 mg/minute whichever is slower) in children under blood pressure, ECG and respiratory rate monitoring as higher rates can cause hypotension, cardiac arrhythmias and respiratory depression. Intramuscular injection has erratic absorption and causes pain at injection site, abscess formation and necrosis, hence avoided. For infusion, phenytoin should be diluted in 0.9% normal saline with dilutions not less than 5mg/ ml and concentrations should not exceed 10mg/ ml. Dextrose or dextrose containing solutions should be avoided for dilutions as phenytoin has decreased solubility and results in precipitation.[4]

Phenytoin is given in a loading dose of 18-20 mg/kg and maintenance dose of 5-8 mg/kg/day in three divided doses or 100 mg TDS. Its therapeutic range is between 10-20 mcg/ml. Some patients remain seizures free at drug levels below reference range while other patients may develop dose related side effects at drug levels within the reference range. Thus "individual therapeutic concentration" has to be determined.[1] Toxic effects are manifested at serum phenytoin levels above 20 mcg/ml.

It follows non-linear kinetics and has a narrow therapeutic index. A small increase in dose results in relatively large increase in serum levels. Therefore the main aim of treatment is to achieve therapeutic efficacy i.e. control of seizures, without toxicity. It is known to have a diverse adverse effect profile such as non-dose related adverse effects like gum hypertrophy, hirsutism, hypersensitivity, megaloblastic anemia, osteomalacia and dose related adverse effects like ataxia, nystagmus, drowsiness, nausea and vomiting. Lethal phenytoin dose is estimated to be 2-5 grams. Treatment is supportive measures as there are no known antidotes to phenytoin toxicity. Stop phenytoin administration, cardiovascular and respiratory support, gastric lavage if required, fluid and electrolyte balance hemodialysis or peritoneal dialysis in adults and total exchange transfusion in children have been tried in some cases.[4] A complete history, inspection for gum hyperplasia in patients, cerebellar symptoms and signs, and knowledge of the full spectrum of clinical presentations of acute phenytoin intoxication would improve diagnostic accuracy.[5]

Our patients presented with symptoms mimicking other diseases i.e., bilateral presenile cataract, encephalopathy and peripheral neuropathy. Here the estimation of serum

drug levels played an important role in confirming phenytoin toxicity and all three cases had serum phenytoin levels of more than 40 mcg/ml. Serum phenytoin measure was done using chemiluminescent immunoassay method. Causality assessment of each of these adverse drug reactions was done by WHO-UMC and Naranjo's algorithm for causality assessment which indicated "Probable" and level 4(b) according to Modifies Hartwig and Siegel severity assessment scale. None of the patients needed intensive care. However with withdrawal of phenytoin treatment, supportive care and change in antiepileptic drug to levetiracetam, the final outcome of all three cases was satisfactory.

In clinical practice, it is important to estimate how long phenytoin should be temporarily withdrawn and when phenytoin therapy might safely be restarted with a limited number of blood samples taken to detect drug levels.[5] Adverse drug reaction monitoring plays a vital role in identifying drug related toxicity and managing them appropriately.

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