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Acute phenytoin toxicity mimicking as acute febrile encephalopathy: A case report and review of literature

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Abstract
Phenytoin is a commonly used drug in paediatric emergency and outpatient treatment in developing countries. However it can produce significant dose-related toxicity because of its zero order pharmacokinetics. Rarely this can produce unusual symptoms like fever, vomiting and altered sensorium masquerading as acute encephalitis. Here we report this unusual presentation of phenytoin toxicity and discuss possible approaches to minimize the possibility of dosing error in prescription of phenytoin.

Keywords: Phenytoin toxicity, Encephalitis, Dosing error.

Introduction
Phenytoin is a common drug used in emergency paediatrics and in outpatient treatment in developing countries for management of generalized tonic clonic seizures. It is a hydantoin-derivative anticonvulsant drug used primarily in the management of complex partial seizures and generalized tonic-clonic seizures.(1)

It acts by voltage-dependent block of voltage-gated sodium channels. Additionally, phenytoin is a class 1b anti-arrhythmic that can be used to treat cardiac arrhythmias.

It has a narrow therapeutic range and wide inter-individual variability in clearance and as a result, therapeutic drug monitoring is often necessary.(1) Dizziness and ataxia are well known symptoms of phenytoin toxicity. In this article we present an unusual presentation of phenytoin overdose.

Case Report
An 11 year old boy presented to the emergency department of our hospital with fever for one day with recurrent episodes of vomiting and altered sensorium. He was a known case of epilepsy with generalized tonic-clonic seizure due to neurocysticercosis with perilesional edema and was on oral phenytoin and tablet acetazolamide for last 5 days prescribed by a private practitioner. Although phenytoin was prescribed at a dose of 5 mg/kg/day, he was inadvertently administered dose of 20 mg/kg/day by his parents as the parents confused the phenytoin dosage with that of acetazolamide. There was no past history of ear discharge, trauma, dog bite or vaccination. On examination at admission, his pulse rate was 94/min, respiratory rate was 26/min and BP in the right arm in a supine position was 116/70 mmHg. He had a generalized erythematous maculopapular rash for the last 1 day. He was also drowsy with a Glasgow coma scale of 11/15 (E3V3M5). Cranial nerve examination including fundus examination were normal. Both pupils were equal in size and normally reacting to light. The tone was increased in all 4 limbs, power was >3/5 in all limbs and deep tendon reflexes were brisk. Bilateral Planters were extensor. Pain sensation was preserved. However, there were no meningeal signs. There was associated nystagmus. Rest of the systemic examination was normal.

Investigations revealed, Hemoglobin-10.5 gm/dl, Total Leucocyte Count (TLC)-10,500/cumm with neutrophils 50% and lymphocytes 50%. Platelet counts - 362000/ cumm, serum sodium-134 meq/l, serum potassium- 4.4 meq/l. Blood urea was 33mg/dl with serum creatinine 0.3 mg/dl. Cerebrospinal fluid (CSF) examination was normal with no cells, protein 22 mg/dl, sugar 72 mg/dl (Blood sugar 100 mg %) and a normal gram stain and a sterile culture. CSF sample for measles, HSV and JE virus was negative. Serum Typhidot IgM and malaria antigen were negative. Dengue serology was non reactive. Serum phenytoin level on the day of admission was 48.3 mcg/L (normal =10-20 mcg/L). It showed a gradual decline with a level reaching 26.15 mg/l on day 6 of admission. Mantoux was negative. Previous CT scan of head showed inflammatory granuloma in right high parietal lobe with perilesional edema suggestive of neurocysticercosis. MRI brain done during the illness showed partial resolution of inflammatory granuloma with perilesional edema compared to previous scans.

Phenytoin was stopped. The child was given a loading dose of valproate and subsequently started on maintenance dose of valproate. Initially, suspecting encephalitis injectable ceftriaxone and acyclovir were started. After excluding meningitis and herpes simplex encephalitis, these drugs were stopped. Supportive therapy in the form of antipyretics, antiemetics and intravenous fluids were given. The child showed normalization of sensorium after 48 hours. He developed excoriation of skin over hands and feet

which subsided by 7th day. On follow up he is seizure free and neurologically normal.

Discussion

Phenytoin is a very commonly used antiepileptic drug in developing countries as it is inexpensive, easily available and has a convenient once a day dosing.

It acts directly on sodium channel to slow the rate of recovery of inactivated state to closed state. By this it increases the threshold for action potentials and prevent repeated firing of neurons. This has the effect of stabilizing the seizure focus by preventing the paroxysmal depolarizing shift that initiates the focal seizures. It also prevents rapid spread of seizure activity to other neurons accounting for its activity in secondary generalized seizure.(2) The vast majority of patients take phenytoin without any adverse effect. However owing to its zero order kinetics and narrow therapeutic index it has the potential to cause toxicity. The normal blood level of phenytoin is between 10-20 mcg/L (total) or 1-2 mcg/L (free drug). Common side effect in pediatric patients were drowsiness, fatigue, ataxia, irritability, rash, gingival hyperplasia. Rare side effects are toxic amblyopia, encephalopathy, AV conduction disorder, megaloblastic (folate-deficiency) anemia. The most frequent neurological findings reported include nystagmus (95%), ataxia (88%), lethargy (22%) and seizures (19%), all of which were seen in the child. Less commonly, movement disorders, ophthalmoplegia, opsoclonus, cerebellar atrophy, reversible focal neurological deficits present as complications of acute phenytoin intoxication from time to time.(3)

In this article, we have described one of the rare side effects of phenytoin i.e. acute febrile encephalopathy.

Infact, the term "phenytoin encephalopathy" was applied by Glaser (1973) to the rare syndrome of increasing intellectual impairment, increased frequency of seizures (Levy and Fenichel, 1965), and focal neurological signs induced by phenytoin and reversed when the drug is stopped. The focal signs may include hemiparesis, hemisensory disturbance, and dysphasia.(4) In our case patient had presented with features of fever, rash and encephalopathy.

In a previous study by Gupta et al, the authors had reported 2 cases of phenytoin toxicity presenting with features of acute meningoencephalitis. The child presented with altered sensorium, terminal neck stiffness, nystagmus decreased motor power, hyperreflexia in both lower limbs with bilateral planters being extensor as in our case though neck rigidity were not present in this child.(2) In another case report by Shukla et al, a 4-year-old female child presented with generalized tonic-clonic convulsions and history of vomiting, irritability and dysarthria of short duration. On examination she was found to be responsive only to painful stimulus, had terminal neck stiffness and bilateral extensor planters. There was history of accidental ingestion of phenytoin.(5)

Patients taking phenytoin are usually taking the drug as a treatment of neurological disorder. Though a meningoencephalitis like presentation of phenytoin toxicity is rare, it needs to be considered in the differential diagnosis of a patient taking phenytoin who presents with obtundation or features suggestive of meningeal irritation.

Moreover, few precautions while prescribing anticonvulsants especially phenytoin can prevent such catastrophic adverse events. First and foremost, the prescription should be as simple and short as possible. Any additional drug, like for cerebral edema should be added only if absolutely necessary to prevent confusion between drugs. Calcium, vitamin D and folate supplements need not be prescribed on the first visit as is a usually observed practice. Sometimes, the drug dispensed from hospital pharmacy is in a different package as compared to the one available from the chemist shops. This has also been observed to confuse parents resulting in inadvertent double dosing. Last but not the least, the treating physician should personally see the drugs dispensed and crosscheck the understanding to parents to minimize dosing errors.

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