CASE REPORT

Acute phenytoin intoxication in a 4-year-old mimicking viral meningoencephalitis

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SUMMARY

We report here the case of a 4-year-old female preschooler who presented to the emergency department with generalised 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 plantars. In view of her clinical presentation, an initial diagnosis of viral meningoencephalitis was made in the emergency room and the child treated accordingly. On subsequent transfer to the intensive care unit (ICU), the parents revealed additional history of an elder sibling taking phenytoin for seizures. Therefore, a suspicion of acute phenytoin toxicity was made and phenytoin levels sent for confirmation. Her serum phenytoin level was 80 µg/mL (normal: 10–20). The child was managed conservatively and discharged after 5 days of hospitalisation. We chose to report this case to highlight the unusual presentation of this rare intoxication.

BACKGROUND

Phenytoin is a commonly prescribed anticonvulsant used to treat most types of seizure disorders and status epilepticus, with the exception of absence seizures. Phenytoin metabolism is dose dependent. Elimination follows first-order kinetics at low drug concentrations, and zero-order kinetics at higher drug concentrations which carries a special risk of dose-related toxicity that is an important issue in emergency medicine.¹ Its wide pharmacokinetic variability and narrow therapeutic range often leads to toxicity which may have varied manifestations. The features of acute poisoning are different from that of chronic.¹ We report the unique case of a child who presented with features of acute phenytoin toxicity mimicking meningoencephalitis.

CASE PRESENTATION

A 4-year-old female child presented to the paediatric emergency room of our tertiary-level referral hospital, with complaints of two episodes of generalised tonic-clonic seizures associated with up-rolling of eye balls and frothing lasting for 10 min followed by a postictal loss of consciousness of 20 min. The parents also gave history of vomiting, rapid eye movements, hypotonia, irritability, dysarthria and dysphagia of 4 days duration. The symptoms were noted by the mother after the child woke up from sleep. There was no history of fever, diarrhoea, cough, cold, trauma, dog bite, toxin exposure or drug intake forthcoming at admission. Past history was non-contributory. The child was

born out of a non-consanguineous marriage, and was fourth in the birth order. Her development was appropriate for her age. Her hemodynamics were stable with a heart rate of 98/min, respiratory rate of 26/min and blood pressure of 96/60 mm Hg. Neurologic examination revealed a Glasgow Coma Scale score of 9, irritability, terminal neck stiffness, horizontal nystagmus, decreased motor power, normal knee and exaggerated ankle jerks bilaterally. Rest of the systemic examination was normal. In view of the above clinical spectrum, initially, a provisional diagnosis of viral meningoencephalitis was made in the emergency room. However, on subsequent transfer to the ICU (after 5 h) the parents informed us that the elder sibling (a 6-year-old boy) was taking phenytoin syrup at 5 mg/kg/day. Thus, a suspicion of phenytoin intoxication was made and serum phenytoin levels sent accordingly for confirmation.

INVESTIGATIONS

Her initial investigations revealed normal blood glucose levels (random blood sugar –108 mg/dL), normal complete blood count, normal blood biochemistry (serum electrolytes, liver function tests, kidney function tests), normal arterial blood gases, electrocardiogram and chest x-ray. Her cerebrospinal fluid was acellular, with protein of 96 mg/dL and sugar of 88 mg/dL. The serum phenytoin levels sent on suspicion of acute phenytoin toxicity was 80 µg/mL (normal 10–20 µg/mL).

TREATMENT

The child was managed conservatively and closely monitored for side effects of the drug, especially cardiovascular and neurological. For her seizures she was given midazolam, and loading and maintenance doses of valproate, as in our unit we often start valproate as first-line agent for generalised tonic-clonic convulsions. No antibiotics were used. The child started showing signs of improvement from day 2 of admission, vomiting and hypotonia resolved, motor power and consciousness improved by day 3. She was able to walk by day 4 of stay although ataxia, tremors and nystagmus persisted with diminished severity. Her repeat serum levels prior to discharge had dropped to 24 µg/mL.

OUTCOME AND FOLLOW-UP

The child was discharged after 5 days of ICU stay after she made complete recovery. At discharge, only mild dysarthria persisted. Repeat phenytoin levels after 1 week of discharge showed no traces of the drug. A MRI of the brain has been planned for

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the child after a gap of 6 months, as cerebellar atrophy may be a late complication in such cases.

DISCUSSION

Phenytoin is hydroxylated and converted to the para isomer of 5-hydroxy-phenyl-5-phenylhydantoin (p-HPPH) in the liver and is excreted as the glucuronide conjugate of p-HPPH in the urine. This is a saturable process. The point at which saturation occurs is unpredictable and varies among individuals. Once saturated, the serum phenytoin concentration rises in a curvilinear manner. This is why small increments in dose can cause a large increase in the serum phenytoin level in many patients. The narrow therapeutic index, the wide interindividual variability in the rate of phenytoin metabolism and clearance, and the saturation (zero-order) pharmacokinetics of phenytoin are responsible for the observed dose-related toxicity.¹

This case was unusual as there was no history of phenytoin intake forthcoming at admission. The case could have easily been missed as meningoencephalitis, and the child could have been started on phenytoin for seizures which could have led to further damage. This effectively points at the importance of history taking, with increased degree of suspicion towards phenytoin toxicity, given the wide spectrum of clinical presentations of phenytoin toxicity. Phenytoin toxicity occurs frequently with the usual central nervous system presentation of nystagmus, ataxia, slurred speech, decreased coordination and seizures. Cardiovascular toxicity has been associated with the intravenous form of phenytoin, but has not been seen with the oral form.² This could probably be the reason for absence of features of cardiovascular toxicity seen in our patient. As phenytoin is a known hepatic enzyme inducer, it may affect the metabolism and serum concentrations of thyroid hormones and cause features of hypothyroidism.^{3–5} Gastrointestinal abnormalities associated with phenytoin toxicity have not been documented in the literature. However, gastrointestinal abnormalities have been associated with hypothyroidism^{6,7} which may occur secondarily in these cases.

Acute phenytoin toxicity is known to manifest with such a diverse array of neurological signs and symptoms that, a high index of clinical suspicion, coupled with estimation of serum phenytoin levels are imperative to elucidate its spectrum. 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, opsochonus, cerebellar atrophy, reversible focal neurological deficits present as complications of acute phenytoin intoxication from time to time.⁸ In adults, the earliest sign of intoxication is nystagmus (level >20 µg/mL) followed by dysarthria and ataxia (level >30 µg/mL). If the level rises above 40 µg/mL somnolence may occur.⁹ Seizures have been reported at levels >30 µg/mL.¹⁰ It is noteworthy in children that the usual toxic side effects, such as nystagmus, occur at high levels only, while ataxia may precede the former.⁹ Chronic phenytoin toxicity may mimic various neurological disorders, like cerebellar and brainstem lesions, or subarachnoid haemorrhage,¹¹ but there have been cases reported of cerebellar atrophy following acute overdose of phenytoin, in the light of which such a possibility has to be kept in mind in patients of acute phenytoin toxicity.¹²

The mainstay of therapy for a patient with phenytoin intoxication is supportive care. Treatment includes maintaining vital

functions, management of nausea and vomiting, and prevention of injuries due to confusion and ataxia. There is no antidote, and there is no evidence that any method of gastrointestinal decontamination or enhanced elimination improves outcome. Activated charcoal should be considered if the patient presents early; however, the role of multiple-dose activated charcoal is controversial. Experimental studies have proven increased clearance rates, but this effect has not been translated into clinical benefit. There is no evidence that any invasive method of enhanced elimination (such as plasmapheresis, haemodialysis, or hemoperfusion) provides any benefit.¹³ Seizures due to phenytoin intoxication are managed by phenytoin withdrawal,¹⁴ benzodiazepines can be used for controlling ongoing seizures.

Learning points

- ▶ Acute phenytoin intoxication may mimic acute viral meningoencephalitis in children.
- ▶ There is no antidote.
- ▶ Seizures are best managed by drug withdrawal, benzodiazepines.
- ▶ Patient should be kept under follow-up to look for neurological complications like cerebellar atrophy.
- ▶ Parents should be educated time and again about the importance of prevention of such injuries as these are best prevented.

Contributors Author contributed to management of the case, reviewing the literature and approved final version of the manuscript.

Competing interests None.

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