Phenytoin-induced encephalopathy in a child
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Abstract:
Phenytoin is a commonly used antiepileptic medication in the pediatric age group, but it has a narrow therapeutic range. Various adverse effects have been reported commonly. We report a relatively rare case of encephalopathy in a child from overdose of injectable phenytoin due to ignorance of the previous treatment. Scrutiny of medical records and history is of utmost importance while administering such medications.

Key words:
Antiepileptic drugs, child, overdosage, phenytoin, side effects

Phenytoin is used extensively as an antiepileptic medication in the pediatric age group. It is not devoid of adverse effects due to narrow therapeutic range. Hence, it is to be administered with great caution. We report a case of a 7-year-old male child with encephalopathy induced by an overdose of phenytoin, which is one of the uncommon side effects.

Case Report
This patient presented to the emergency department with features of altered sensorium without fever. The patient was a known case of seizure disorder, with an onset at an age of 2 years. The child received antiepileptic medications after which seizures were well-controlled, but the medications were discontinued by the parents. Thereafter, the child received medications from various sources including herbal and ayurvedic preparations. The patient had associated developmental delay and had frequent recurrences of seizures. During this episode, before presenting to our hospital, the child received treatment at two institutions. A loading dose of injectable phenytoin (20 mg/kg followed by 10 mg/kg) was given at both hospitals without checking the previous records. The total dose of phenytoin thus received was 60 mg/kg. Cerebrospinal fluid examination report presented was normal (Phenytoin levels were not done).

On examination, the child was in an altered state but did not have any neck rigidity. There was no cranial nerve deficit but had nystagmus. Plantar reflex was flexor; tendon reflexes and tone were normal. These findings ruled out any infective process. The rest of the systemic examination was also normal. A possibility of phenytoin overdose was considered. The patient was treated with injectable valproate, and seizures were controlled. A magnetic resonance imaging (MRI) of the brain was performed which revealed a lobulated mass likely to be hamartoma (old lesion). Serum phenytoin levels were very high (56 µg/ml), and a diagnosis of phenytoin-induced encephalopathy was established.

Causality analysis was done using the World Health Organization-Uppsala Monitoring Center causality categories showed probable/likely association. According to the Hartwig severity assessment scale, the event was Level 4. Further, as per the Naranjo algorithm, the event has a score of 6 which is probable adverse drug reaction. The patient regained consciousness on the next day and was active and playful without any neurodeficit. The patient was free of seizures on follow-up until next 1 month. A repeat MRI was advised to know about fate of intracranial mass (hamartoma) but was refused by the parents.

Any drug has potential for toxicity which may occur due to errors in prescribing, dispensing, or administration and/or increase in doses and/or change in brands/formulations of the drug. Phenytoin toxicity can be precipitated by an acute overdose, altered physiological state in disease.
conditions, interindividual variability, drug interactions, and genetic mutations in the cytochrome P450 enzyme. The well-known manifestations of phenytoin overdose are nausea, vomiting, dizziness, vertigo, and lethargy. Altered mental status, confusion, slurring of speech, nystagmus, diplopia, ataxia, and dystonia are neurotoxic features that have been reported. Rapid intravenous dosing may lead to cardiac toxicities such as hypotension and arrhythmias which may be fatal. Phenytoin is primarily metabolized in the liver by para-hydroxylation, followed by glucuronic acid conjugation. The metabolism of phenytoin is complex and follows the first-order kinetics at low doses; however, after saturation of the enzyme, it changes to zero-order kinetics. Thus, the potential for toxicity is high in overdosages. The therapeutic dose of phenytoin is a loading dose of 20 mg/kg, followed by 5–8 mg/kg/day as a maintenance dose. The therapeutic level is very narrow (10–20 µg/ml) and the toxicity manifests above the levels >20 µg/ml. Levels >50 µg/ml are associated with a high risk of mortality.

Our patient received the injectable dose twice with a cumulative dose of 60 mg/kg over a short span of 12 h, resulting in acute toxicity. This case highlights the importance of scrutiny of medical records prior to initiating treatment in sick children. As the patient had received treatment at multiple institutions, the further course of action should have been initiated after a thorough check of previous records. The dosages should have been scrutinized before labeling the case as refractory to treatment. Uncommon adverse reactions and drug toxicity should also be considered, in cases where common etiologies are unable to explain the clinical condition. It should be remembered that every drug has a potential of toxicity and uncommon adverse effects are also encountered in clinical practice.

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Conflicts of Interest
There are no conflicts of interest.

References
1. Gupta V, Yadav TP, Yadav A. Phenytoin toxicity presenting as acute meningo-encephalitis in children. Neurol India 2011;59:66-7.
2. Lowry JA, Vandover JC, DeGreeff J, Scalzo AJ. Unusual presentation of iatrogenic phenytoin toxicity in a newborn. J Med Toxicol 2005;1:26-9.
3. Sharma B, Handa R, Prakash S, Nagpal K, Gupta P. Phenytoin toxicity presenting as encephalopathy with fatal outcome: A case report. J Neurol Res 2013;3:184-6.
4. Mehndiratta S. Pediatric dosing errors due to variable drug formulations. J Pharmacol Pharmacother 2014;5:254-5.
5. Su CM, Kung CT, Wang YC, Lu CH. Life-threatening cardiotoxicity due to chronic oral phenytoin overdose. Neurol India 2009;57:200-2.
6. Hwang WJ, Tsai JJ. Acute phenytoin intoxication: Causes, symptoms, misdiagnoses, and outcomes. Kaohsiung J Med Sci 2004;20:580-5.