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Case Report

Paradoxical Seizures: It Could be Phenytoin Toxicity. A Short Communication

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Abstract
Phenytoin is one of the frequently used antiepileptic drug for control of generalized tonic-clonic and complex partial seizures. We present a case of phenytoin toxicity which presented as a breakthrough seizure and exacerbation in the frequency of seizures. This less well known clinical syndrome "paradoxical seizure", may or may not be accompanied by other signs and symptoms of phenytoin toxicity and a high index of suspicion is required to diagnose this condition. Dose de-escalation in these cases leads to decrease in seizure frequency and cessation occurs with reduction in serum concentration of the drug. This case report reemphasizes the importance of timely TDM (Therapeutic Drug Monitoring) for early diagnosis that can prevent dreadful complications especially in cases where obvious signs and symptoms toxicity are absent.

Keywords: Paradoxical seizures; Phenytoin toxicity

Background
Phenytoin is one of the widely prescribed antiepileptic drug in India due to its low cost and easy availability [1]. The efficacy of this drug in achieving seizure control in patients with epilepsy is good. It is commonly used for treatment of tonic-clonic and complex partial seizures in both children and adults. Phenytoin toxicity is an uncommon finding in clinical practice [2]. The predisposing factors include hypoalbuminemia, chronic renal failure, hepatic dysfunction and drugs which interfere with phenytoin metabolism [2].

A good correlation usually is observed between the total concentration of phenytoin in plasma and its clinical effects especially tonic-clonic seizures [3]. Thus, control of seizures generally is obtained with total concentrations above 10µg/ml, while toxic effects such as nystagmus, cerebellar symptoms like confusion, behavioural changes and ataxia develop at concentrations above 20µg/ml [4]. However, a less well-known phenomenon "paradoxical seizures" has also been described which is a situation where in the seizure frequency increases, as the blood level of the antiepileptic drug increase [5]. This high concentration is associated with no or few signs and symptoms of toxicity, and thus the paradox. This paradox makes it difficult to suspect toxicity in the patient.

Earlier in 1968, Patel and Crichton described toxicity and increased seizure frequency in children, both of which improved with decreased dosages of phenytoin [6]. But, in this study serum drug levels were not reported. Similar observations were made by Lascelles et al (1970) with partial blood concentration data [7].

Case Presentation
A four-year old male child, known case of idiopathic epilepsy since one year, on syrup phenytoin at dose of 8mg/kg/day (7.5ml BD) with good compliance, presented to paediatric emergency room with breakthrough seizure with afebrile onset. The seizure lasted for 2-3 minutes and followed by postictal confusion. At presentation, the parents reported that the child also had altered sensorium since one day. There was no history of fever, headache, vomiting, head trauma, respiratory distress or neurological deficit. There was no neck rigidity or other signs of meningeal irritation. The Glasgow coma score was E1M5V3.

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Child was admitted in a government hospital closer to his hometown for one day, where he was administered levetiracetam at the dose of 20mg/kg/day and phenytoin at the dose of 8mg/kg/day. Subsequently child was brought to our centre (tertiary care referral centre and teaching hospital) where child was continued on Phenytoin 8mg/kg/day in two divided doses and syrup levetiracetam at dose of 20mg/kg/day in 2 divided doses for control of seizures.

But child continued having seizures. In view of uncontrolled seizures, dose of levetiracetam was increased to 50mg/kg/day in 2 divided doses. Haematological and biochemical investigations were ordered. The blood samples were also sent to the TDM (Therapeutic Drug Monitoring) laboratory to rule out sub-therapeutic concentration of phenytoin.

Past History

The Child had completed the immunization schedule as per National Immunization Schedule (NIH) for his age. The developmental history was normal. However, the child was a known case of idiopathic epilepsy and had been receiving treatment at our centre.

The child has presented previously to the pediatric emergency of our centre in May 2016 with afebrile status epilepticus. He was intubated, ventilated and seizures were managed with phenytoin loading followed by maintenance dose at rate of 8mg/kg/day. The investigations done during admission were CSF (which was not suggestive of meningitis), MRI brain (which was with-in normal limits and did not suggest structural or organic lesions), serology for neurocysticercosis and PCR for HSV (which were negative).

In the light of these findings, the diagnosis of idiopathic epilepsy was made and the child was discharged from our hospital on syrup phenytoin 8mg/kg/day (7.5ml BD).

Six months before the index admission, there was history of another episode of seizure for which child was admitted and treated in local hospital (of which no further details were available).

In the index episode, the child presented to us in a stuporous condition with breakthrough seizures and continued to have seizures despite treatment.

Investigations:

The following investigations were ordered for the cause of breakthrough seizures.

- Serum Albumin: 2.7g/dl (normal albumin levels= 3.5-5 g/dl).
- Other haematological and biochemical parameters were within normal limits.
- Plasma Phenytoin levels request was sent to the TDM laboratory for suspected inadequate response.

The sample was analysed using HPLC-UV method and the total phenytoin concentration was found to be 34.91 mg/L (normal therapeutic range 10-20 mg/L or µg/ml). In view of hypoalbuminemia (serum albumin 2.7 g/dl), Sheiner-Tozer formula was used to correct phenytoin concentration for low serum albumin.

Adjusted Phenytoin concentration = measured total concentration / [(0.2 x albumin) + 0.1]

The corrected concentration was found to be 54.55µg/ml, which was above the therapeutic range. Subsequently, the clinician was advised to with hold the drug based on plasma concentration and send serial blood samples for drug analysis with close clinical monitoring. The serial measurements of phenytoin concentration are depicted in Table -1.

TDM Sample number	Plasma phenytoin concentration (Corrected for low albumin)
283	54.55 µg/ml
284	45.91 µg/ml
290	41.48 µg/ml
291	26.55 µg/ml

Table 1: *Paradoxical phenytoin toxicity: serial plasma phenytoin levels.*

There was continued occurrence of seizure with same frequency till day 2 of stoppage of phenytoin, after which frequency of seizures reduced decreased and seizures stopped completely on day 5 of stoppage of phenytoin.

WHO-UMC probability scale [8] was applied for causality assessment. There was a temporal association between the increase in seizure frequency and serum concentration of phenytoin and hence the causality was labelled as 'probable'. After withholding phenytoin, seizures resolved without any additional intervention. The graphical representation of correlation of time of control of seizure and plasma phenytoin levels is shown in Figure -1.

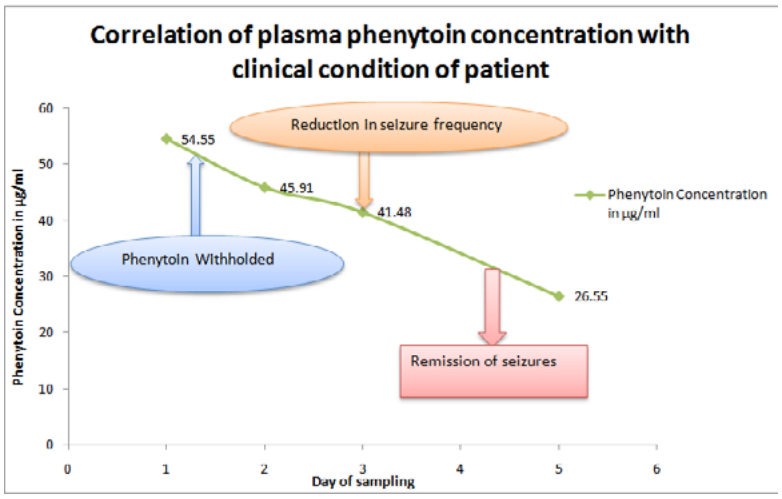

Figure 1: *Day-wise diagrammatic representation of plasma phenytoin levels and clinical correlation.*

Differential Diagnosis

Before the receipt of the report on plasma phenytoin concentration, the following differential were kept in mind

- Meningeal/CNS infection
- Structural epilepsy

Management:

Based on feedback from the TDM team, the treating physicians withheld the phenytoin administration and sent blood samples for serial analysis along with close clinical monitoring. Levetiracetam was continued at the previously administered dose.

Outcome:

The seizures resolved with fall in plasma levels to 26.55 µg/ml without any additional intervention. The child was discharged after few days of seizure control on D9 of hospital admission.

Discussion:

Phenytoin toxicity presenting as paradoxical increase in seizure frequency is a rare entity. Usually phenytoin toxicity presents with cerebellar signs and symptoms like vertigo, nausea, drowsiness, ataxia, gait abnormalities, nystagmus but sometimes an increase in seizure frequency with a mildly altered sensorium may be the only presenting symptom of drug toxicity as in this case [9].

The exact mechanism of these paradoxical seizures is unknown. However, an animal study by Okada et al [10] studied effect of non-toxic and toxic concentrations of phenytoin on rat brain monoamine levels. They reported that supratherapeutic concentrations of phenytoin leads to decrease in levels of monoamine in striatal and hippocampal areas of brain in concentration dependent manner leading to onset of generalized tonic clonic seizures. He suggested that dysfunction of monoaminergic transmission may be partially involved in paradoxical seizures due to phenytoin toxicity.

Phenytoin has a narrow therapeutic range of 10-20µg/ml. At plasma concentration below 10µg/ml, elimination of phenytoin follows first order kinetics [1]. However, at higher concentrations, even in therapeutic range (10-20µg/ml),

the metabolic pathway gets saturated and elimination shifts from first order to zero order kinetics [2]. There are reports of paradoxical seizure with phenytoin in the literature however the concentration at which it may occur differed from case to case (ranged from 38.3 to 46.5 µg/ml) [2,11]. In our case, the initially obtained total concentration was 34.91µg/ml but since the child was hypoalbuminemic the corrected phenytoin concentration was 54.55µg/ml, which is similar to the earlier reports in literature. It appears that most of cases occur beyond 40 µg/ml and risk factors associated with increased levels are the hypoalbuminemic states like nephrotic syndrome, renal failure, hepatic cirrhosis, burns etc.

This case report re-emphasises that though rare, paradoxical seizures due to phenytoin toxicity could have a misleading presentation. Hence, it requires a high index of suspicion since it could be easily misdiagnosed as breakthrough seizures due to subtherapeutic phenytoin concentration and often attributed to drug non-compliance. Further administration of phenytoin to treat this condition may aggravate the drug toxicity leading worsening of clinical condition. Therefore, high index of suspicion and timely TDM could prevent such adverse event and thus prove extremely useful in clinical management of such cases.

Conclusion

Paradoxical seizure due to phenytoin toxicity should be considered as one of the important differential diagnosis in patients presenting with breakthrough seizure and with a history of treatment with phenytoin. TDM is instrumental in making the correct diagnosis and early withholding of drug can prevent dreadful complication and death.

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