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Paradoxical Seizures in Phenytoin Toxicity

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ABSTRACT

Phenytoin toxicity is an uncommon problem seen in clinical practice. The predisposing factors for toxicity are hypoalbuminemia, chronic renal failure, hepatic dysfunction and drugs which interfere with phenytoin metabolism. Common manifestations of toxicity, like confusion and ataxia, are well known. A less well known phenomenon is paradoxical seizures. In this condition, seizures develop as the serum phenytoin level rises and decrease in frequency as levels drop. It may or may not be accompanied by other features of toxicity. We present three patients with paradoxical seizures; their serum phenytoin levels were 43.5 mcg/mL, 46.5 mcg/mL and 38.3 mcg/mL. In all cases, seizures were controlled by withdrawal of phenytoin and reduction of drug levels.

Keywords: paradoxical seizures, phenytoin toxicity, epilepsy, drug levels, phenytoin withdrawal

INTRODUCTION

Merritt and Putnam[1] first introduced phenytoin for medical use because of its striking ability to suppress electroshock convulsions in laboratory animals. Although the drug is a widely used anti-convulsant, overdose is not a common clinical problem. There are marked variations among individuals with respect to phenytoin levels, where toxicity may occur[2-7]. Nystagmus appears at levels about 20 mcg/mL, ataxia at 30 mcg/mL and drowsiness and dysarthria beyond 30 mcg/mL. Beyond 40 mcg/mL, there is increasing disorientation, hyperreflexia, myoclonus, extensor rigidity, opisthotonus and paradoxical seizures[2,8-11].

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CASE REPORTS

Case 1

LSH is a 26-year-old Chinese female with mental retardation and cerebral palsy. She had childhood seizures since eight months of age. These seizures were generalised tonic-clonic in nature and she was treated with phenytoin 300 mg o.n. by her family doctor. Initially her seizures were well controlled, but they became more frequent, about 2 to 3 times a month prior to her hospitalisation. The patient's mother claimed compliance to medication. The patient was admitted because she had a convulsion on the day of admission. Two weeks prior to admission, she was noted to be rather restless and agitated. On examination, she was drowsy and opened her eyes spontaneously. She was non-communicative but moved all four limbs spontaneously. No other neurological deficits were detected. There was no nystagmus. She had another convulsion while in the ward, lasting about 30 seconds. There was jerking of all four limbs with up-rolled eyes and clenched teeth. This was followed by post-ictal drowsiness and urinary incontinence.

Serum phenytoin levels at that time was 43.5 mcg/mL. She was not on any other medication and biochemical tests (urea and electrolytes and liver function tests) were normal. Her oral phenytoin was stopped and she did not have any more seizures. It was subsequently re-instituted when serum levels fell to 16.1mcg/mL).

Case 2

TST is a 38-year-old male Chinese who developed recurrent seizures after an attack of viral encephalitis a year earlier. His seizure frequency was once every 3 months. At a phenytoin dosage of 300 mg o.n., his serum levels were only 2.3 mcg/mL and hence his dosage was increased to 330 mg o.n.. His corresponding serum phenytoin level was 18.4 mcg/mL. As he continued to have seizures twice a month, his dosage was progressively increased to 360 mg o.n. and then to 390 mg o.n.. On review in the Outpatient Clinic a month later, he complained of a seizure the day before, lasting a few minutes. He claimed compliance to medication.

On examination, he was alert and conscious. He had bilateral horizontal nystagmus. He was unable to tandem walk. There were no other neurological deficits. His serum phenytoin level at that time was 46.5 mcg/mL. His phenytoin was stopped and he did not have any more seizures. Oral phenytoin was re-started when his serum levels were less than 15 mcg/mL.

Case 3

TCK is a 56-year-old male Chinese who had a fall in March 1995 and developed a left parietal haemorrhage. Craniectomy and clot evacuation were done. He had a history of chronic ethanol ingestion and was diagnosed to have alcoholic liver disease in 1990. He had been drinking since the age of 16 years and drank three bottles of beer a day. He stopped

drinking about 3 months prior to admission. He developed generalised seizures in June 1996 and was treated with phenytoin 300 mg o.n.. His seizures occurred once every 2 months. He was admitted because of nightly seizures for the preceding 2 weeks. These were witnessed by his wife, and described as generalised tonic-clonic with clenching of teeth and up-rolled eyes. Each seizure lasted 5 minutes and was accompanied by post-ictal drowsiness.

On examination, he was alert and conscious. He had bilateral horizontal nystagmus and dysmetria. There was a right upper motor neuron facial palsy and power on the right side was 4/5. Tone was increased in the right upper and lower limbs and there was an extensor plantar response. He had spider naevi and palmar erythema. There was no hepatosplenomegaly and no other stigmata of chronic liver disease.

His phenytoin level on admission was 38.3 mcg/mL. Liver function tests: total protein 69 g/L albumin 41 g/L bilirubin 7 μmol/I alkaline phosphatase 288 U/L alanine transaminase 30 U/L aspartate transaminase 52 U/L. Urea and electrolytes were normal. Phenytoin was stopped and there were no more seizures. It was re-started when his phenytoin level fell to 9 mcg/mL.

DISCUSSION

The three notable features of paradoxical seizures are as follows[2,8-11]: (a) all patients had underlying epilepsy; (b) they were all on continuous phenytoin treatment, and (c) seizures occurred with increasing drug levels and decreased as the levels fell.

These features were well demonstrated in our patients: they all had underlying epilepsy; all were on continuous phenytoin treatment; the duration varied from more than 20 years in the first patient and to three months in the third patient. The typical history is that of an epileptic patient who, because of increasing seizures, increased his dose of phenytoin. This led to even more seizures and an even higher dose of phenytoin being used. In all cases, seizures were controlled by withdrawal of phenytoin and reduction of drug levels.

Troupin and Ojemann[2] reported that the usual toxic features of phenytoin overdose were rarely seen in patients with paradoxical seizures. Nystagmus was found in only two cases (25%) out of eight and ataxia in three (38%). The low incidence of nystagmus might be due to the slowing of saccadic eye movements at high drug concentrations. In the series by Stilman and Masdeu[9], toxic effects were more common: of five patients, four (80%) had ataxia, two (40%) had nystagmus and four (80%) had behavioral changes such as disorientation and lethargy. Nonetheless, the numbers from these studies were too small for any reliable conclusion to be made.

The underlying mechanism of paradoxical seizures remains uncertain. Since only a small number of patients showed this effect, it was postulated that an underlying mechanism might exist, such as the underlying cause of the epilepsy. Phenytoin enhancement of a pre-existing metabolic derangement, structural lesion or phenytoin induced cerebellar degeneration[2,3,6-8] might play a role in paradoxical seizures.

CONCLUSION

Paradoxical seizures may be accompanied by other features of toxic overdose. Treatment requires withdrawing the drug and not increasing it. Serum levels should be monitored before reinstating phenytoin therapy. The potential presence of paradoxical seizures should not discourage a gradual increase in phenytoin dosage as is deemed necessary for seizure control. The clinician must be aware of the predisposing factors for phenytoin toxicity such as hypoalbuminemia, chronic renal failure, hepatic dysfunction and drugs which inhibit phenytoin metabolism. We recommend checking serum levels in epileptic patients who develop more seizures despite a higher drug dosage.

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