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Phenytoin toxicity presenting with acute visual loss and acute delirium, a case report

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Abstract

Phenytoin is a widely prescribed antiepileptic agent for both focal and generalized seizure. We report a case of a 20-year-old man with focal epilepsy presented with acute bilateral visual loss, and delirium. His random phenytoin serum concentration on admission was 43.6 mg/L, well above the recommended therapeutic range of 10-20 mg/L. Extensive investigations have ruled out other vascular or demyelinating causes. His visual symptoms completely resolved after discontinuing phenytoin for 84 hours. This case shows that acute phenytoin toxicity can result in reversible visual failure.

Keywords: Phenytoin toxicity, visual loss, epilepsy, pharmacokinetics, side effects, adverse drug event, AED, antiepileptic drug

CASE REPORT

A 20-year-old man with underlying focal epilepsy presented to the emergency department with acute bilateral visual loss that was first noted in the right eye, followed by the left 12 hours later, resulting in a fall at his bathroom. He denied any headache, orbital pain, fever or seizure prior to that. He developed a right tonic seizure in the emergency department, which was aborted by intravenous diazepam.

The patient was diagnosed to have focal epilepsy at the age of 17 years. He has right upper limb tonic to bilateral tonic-clonic seizures. His previous EEG and MRI brain were normal. He was on oral phenytoin 300 mg OD and sodium valproate 600/400 mg BD. His seizure was uncontrolled, affecting his work performance.

On examination, his pupils were 3 mm in diameter and reactive to light. His visual acuity was poor with light perception only. There was bilateral horizontal nystagmus but no other cerebellar signs. Ophthalmological examination revealed a visual acuity of 2/6 and tunnel vision in both eyes, but no blurred disc margin. Urgent CT brain showed no focal brain lesion. Full blood counts and serum electrolytes were normal. Random phenytoin and valproic acid serum concentrations were 43.6 mg/L and 14.9 mg/L respectively (Therapeutic range of phenytoin: 10-20 mg/L; and valproic acid, 50-100 mg/L). His phenytoin was discontinued. On further questioning, the patient admitted to double his phenytoin dose, and increased sodium valproate to 600/800 mg twice daily for the past three weeks, to alleviate seizure attacks in his new workplace.

About 15 hours later, the patient developed acute confusion and aggression that required haloperidol injection. On the third day of admission, the patient became restless again and complained of severe abdominal pain localized to the left lumbar region. Abdominal ultrasound and urine study were negative. The pain resolved with parenteral tramadol.

MRI brain was performed to exclude demyelinating disease and posterior reversible encephalopathy syndrome, and was reported as normal. Lumbar puncture showed no evidence of infection or inflammation. Ictal blindness was considered unlikely because of atypical presentation of prolonged blindness without other associated motor phenomena; however, an urgent EEG was not performed to rule out this possibility.

After discontinuing phenytoin for about 66 hours, the patient's vision improved but still fluctuating. He started recognizing faces and there was no further delirium episode. At 84 hours after phenytoin dose, the serum concentration was 27.4 mg/L and his visual acuity was back to normal at 6/6 in both eyes. (Refer to Figure 1) The patient was discharged well on day 5 with sodium

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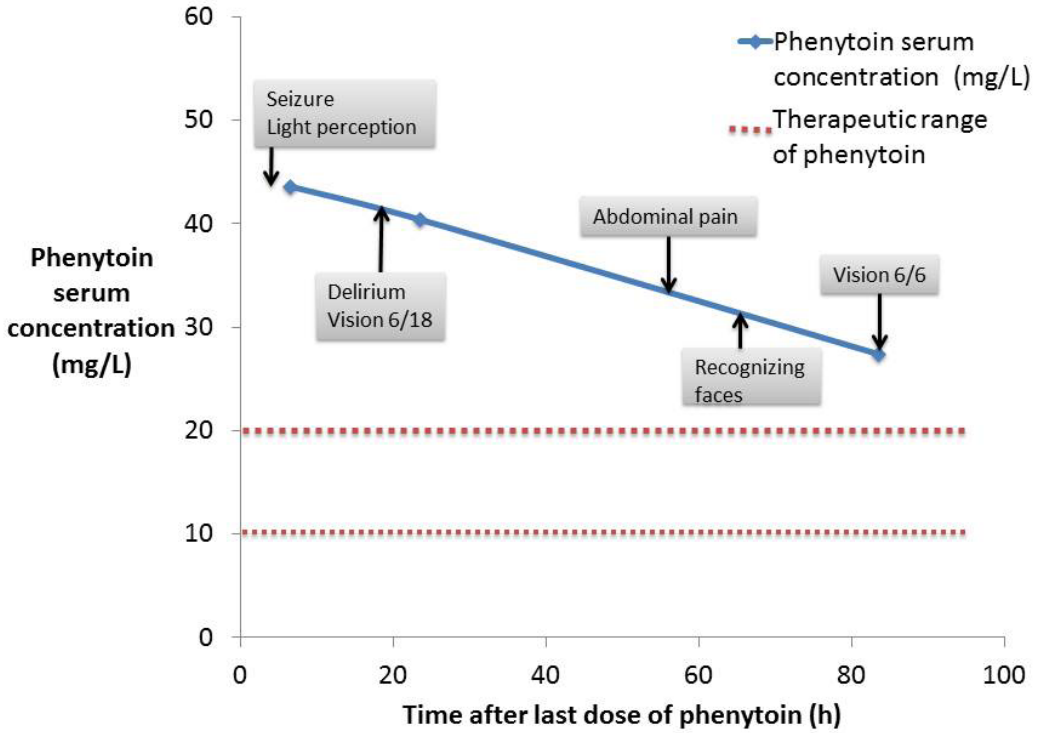

Figure 1. Time course of phenytoin serum concentrations and associated adverse events

valproate 400 mg BD and carbamazepine 200 mg BD. On follow-up one week later, phenytoin serum concentration was undetectable, and his nystagmus had fully resolved.

DISCUSSION

Acute phenytoin toxicity is a rare clinical condition[1], and is most commonly encountered during rapid intravenous loading dose, or excessively high daily dose administration, drug-drug interactions or concomitant liver disease.[2]

Phenytoin exhibits Michaelis-Menten kinetics in its metabolic pathway[3], and enzyme-substrate-binding sites can become saturated. As phenytoin accumulates in the body, this reaction displays a "switch-like" transition from low to high reaction rate, causing a disproportionate increase in phenytoin serum concentrations from even a small increment in dosage.

The presentations of acute phenytoin toxicity include unsteady gait, dizziness, vomiting, slurred speech, and drowsiness.[4] Nystagmus is an important clue to diagnosis of phenytoin toxicity that should not be missed. These symptoms tend to be non-specific, and may be mistaken as posterior circulation infarct. It is uncommon to have phenytoin-induced acute visual loss. Thakral *et al.* described a case of acute blurred vision and xanthopsia, following an intravenous phenytoin loading dose of 1g.[5] Similar to the presentations of our patient, the visual acuity of the patient was diminished and concentric visual field defect was observed.

In this case report, the patient had doubled his daily phenytoin doses for the past 3 weeks prior to the onset of symptoms. The casual relationship between phenytoin and sudden visual loss was assessed using Naranjo Adverse Drug Reaction Probability Scale.[6] A Naranjo score of 9 indicates a definite phenytoin-induced adverse drug reaction, as evidenced by the temporal relationship, elevated phenytoin serum concentration, and resolution of symptoms following phenytoin discontinuation. Furthermore, the possibilities of cerebral infarct, infection or demyelinating disorder have been excluded by the normal MRI brain and cerebrospinal fluid study.

The mechanism of phenytoin-induced visual loss is not entirely understood. Phenytoin exerts its anticonvulsant effect mainly by blocking voltage-sensitive sodium channels in the neurons, especially the neurons in the brainstem and cerebellum.[7] At higher concentrations, phenytoin delays activation of outward potassium currents in nerves and prolongs the neuronal refractory period.

A previous case report on patients with phenytoin-induced visual disturbance demonstrated a prolonged P100 latency in flash visual evoked potential, suggesting its toxic effect at the retina level.[5] In addition, phenytoin may enhance γ-aminobutyric acid (GABA) transmission in the retina, causing visual loss similar to that of vigabatrin, although this mechanism is not yet fully established.[8]

Other symptoms of acute phenytoin toxicity include delirium and abdominal pain; usually occur at drug level of more than 40 mg/L.[9] Paradoxically, a very high phenytoin serum level can also be associated with seizures.

In this case, valproic acid displaces phenytoin at the protein binding sites, causing an increased free fraction of phenytoin, even though the total drug concentrations measured remain unchanged.[2,10] Conversely, phenytoin, an enzyme inducer of UGT in the metabolism of valproic acid[13], reduces valproic acid serum concentrations despite an increased dosage.

In conclusion, this case shows that acute phenytoin toxicity can result in reversible visual failure. Early recognition of phenytoin toxicity is imperative to avoid worsening of symptoms. A meticulous drug history and therapeutic drug monitoring of phenytoin should be considered when an epilepsy patient presents with unexplained neuropsychiatric or visual symptoms. The general management of acute phenytoin toxicity involves withholding the offending medicine and providing supportive care.[11]

DISCLOSURE

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