

Phenytoin-induced Hypothermia in a Patient with Mental Retardation

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Citation

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Abstract

Background: Phenytoin toxicity presenting as hypothermia has been reported in patients with mental retardation (MR), without causative explanation. We report a case in a patient with adrenal insufficiency.

Case Report: A 50-year-old man with a history of MR and seizures was found lethargic. Medications included phenytoin and phenobarbital. Physical examination was unremarkable except for somnolence and hypothermia. The serum phenytoin level was 37 µg/mL (147 µmol/L). A cosyntropin stimulation test showed adrenal insufficiency. No infectious or inflammatory conditions were identified. The patient improved with supportive care, antibiotics and steroids.

Discussion: The mechanism of phenytoin-associated hypothermia is unknown. It may be centrally mediated, or phenytoin may exert an indirect effect on hepatic steroid clearance leading to relative adrenal insufficiency.

Conclusion: Significant hypothermia may occur with phenytoin toxicity. Clinicians should be alerted to this possibility and check a core temperature on patients at risk.

INTRODUCTION

Phenytoin toxicity typically presents with ataxia and nystagmus, but a wide range of symptoms may manifest. Hypothermia is a rarely described condition occurring in the setting of phenytoin toxicity. Two previous case reports suggest a relationship between a history of mental retardation (MR) and the development of hypothermia in patients manifesting phenytoin toxicity (1, 2). We report a case of phenytoin-associated hypothermia in a patient with MR who had documented adrenal insufficiency, presumably due to phenytoin toxicity.

CASE REPORT

A 50-year-old white male resident in a group home was found to have an elevated serum phenytoin level during a routine visit to his primary care provider. The patient had no known drug allergies or significant prior adverse drug reactions. His daily medications included bethanechol 15 mg TID, terazosin 4 mg BID, docusate sodium 100 mg BID, ranitidine 150 mg BID, trazodone 200 mg qhs, olanzapine 20 mg qhs, and zinc oxide topical ointment BID. Phenytoin 125mg TID had been added to this regimen one month prior to this presentation for the treatment of new onset seizures of undetermined etiology. There were no other recent medication changes reported by the group home staff. The

patient did not use tobacco, alcohol or illicit drugs.

Significant past medical history included MR, new onset seizure activity, hepatitis B, chronic cellulitis of the lower extremities, and dysphagia for which a percutaneous enterogastric PEG tube had been inserted one year before. At baseline, he had limited linguistic ability but was alert and able to communicate. His global functioning had declined significantly in recent years and he had been unable to ambulate for the past year.

Several days after his visit to the primary care physician, the patient was noted by the group home staff to be less responsive than usual and was taken to the local emergency department (ED) for evaluation. On arrival to the ED he was lethargic, unable to follow commands, and minimally responsive to environmental stimuli. The following vital signs were recorded: blood pressure: 100/66 mm Hg; heart rate: 44 beats per minute; respiratory rate: 10 breaths per minute; rectal temperature: 33.1°C (91.6° F); capillary blood glucose: 65 mg/dL (3.6 mmol/L). The physical examination was otherwise unremarkable except for a depressed level of consciousness.

An initial serum phenytoin level was elevated at 37 µg/mL. Other diagnostic laboratory studies included a serum

chemistry panel: sodium 134 mEq/L; potassium 4.3 mEq/L, chloride 104 mEq/L; CO₂ 32 mmol/L; glucose 165mg/dL; blood urea nitrogen 7 mg/dL; creatinine 0.8 mg/dL; calcium 8.1 mg/dL; phosphorus 3.5 mg/dL; creatine phosphokinase 4 IU/L; CK-MB Index 3; troponin I 0.01; aspartate aminotransferase 22 IU/L; alanine aminotransferase 17 IU/L; alkaline phosphatase 112 IU/L; total bilirubin 0.3; lactate 1.8 mmol/L. Serum amylase and lipase values were elevated at 460 and 324 U/L, respectively. The complete blood count was within normal limits with the following values: white blood cell count 6.8/μL; hematocrit 35.7%; platelet count 206,000/μL.

Initial imaging studies included a chest radiograph which showed mild bibasilar atelectasis, and a computed tomography (CT) scan of the brain which showed no acute change from prior studies. A right upper quadrant ultrasound did not show any evidence of cholelithiasis. A CT scan of the abdomen showed mesenteric stranding of undetermined significance, a right renal cyst, and a PEG tube in place. A bedside electroencephalogram demonstrated absence of convulsive activity.

Immediate treatment in the ED included intravenous glucose, ceftriaxone 2 grams and levofloxacin 750 mg after blood and urine cultures were obtained, and intravenous fluid boluses of normal saline followed by dopamine and norepinephrine infusions for hypotension (blood pressure: 65/31 mmHg) during rewarming. With the aid of an external warming blanket the patient's core temperature rose to 37°C (98.6° F) over a period of 12 hours. While in the ED the patient had several episodes of coffee-ground emesis and was endotracheally intubated for airway protection. The patient was admitted to the intensive care unit.

On the first admission day, the patient was weaned from pressure support and he remained hemodynamically stable. A repeat chest radiograph showed bilateral pleural effusions, presumed secondary to aggressive hydration and congestive heart failure. Oxygen saturation improved with gradual diuresis and he was extubated on hospital day five. Testing for occult blood in the stool was negative and gastric lavage did not demonstrate any active bleeding. He was kept nil per os (NPO) and continued on maintenance IV fluids for chemical pancreatitis. His hematocrit dropped to a nadir of 25% during this hospital stay. A repeat CT scan of the abdomen did not show any evidence of pancreatic hemorrhage. The results of blood and urine cultures were negative, however, the patient was treated with a course of piperacillin-tazobactam and vancomycin for presumed

sepsis. Phenytoin was discontinued and phenobarbital was started for seizure prophylaxis. Sedatives were discontinued after extubation without any improvement in mental status. A serum cortisol level was drawn on hospital day one, which was 12.4 μg/dL. A cosyntropin stimulation test was done on day two, the patient was found to have adrenal insufficiency, and he was treated with a seven-day course of intravenous hydrocortisone. He was discharged to the group home after ten days in hospital.

DISCUSSION

Core body temperature is known to affect the pharmacokinetics of phenytoin metabolism. Two case reports describe phenytoin toxicity after drug administration to hypothermic patients (3,4), and one study of the effect of therapeutic hypothermia on phenytoin pharmacokinetics, showed significantly higher plasma concentrations and reduced elimination during hypothermia in 14 patients with brain damage (5).

Two prior case reports suggest that the reverse may also occur, and that phenytoin toxicity may produce hypothermia. In the first case, (1) hypothermia was presumably the sole manifestation of phenytoin toxicity, whereas in the second, (2) the patient exhibited ataxia, slurred speech and lethargy. Hypothermia has also been induced in mice by injection of either diphenylhydantoin or carbamazepine (7).

The mechanisms by which different anticonvulsants might produce hypothermia remain unelucidated. There is some evidence from studies in animals to support a hypothesis that this is centrally mediated. For example, AMPA/ kainite receptor antagonism (7) and GABA receptor stimulation (8) have both been shown to induce hypothermia in mice.

Alternatively, phenytoin may produce hypothermia indirectly via induction of hepatic cytochrome P450 enzymes and stimulation of steroid clearance, which could induce or exacerbate adrenal insufficiency in susceptible patients (6). Adrenal insufficiency was not found in either of the two previously reported cases of hypothermia and phenytoin toxicity. However one patient received hydrocortisone prior to a cosyntropin stimulation test (2), and no tests of adrenal function were reported for the other (1). The subject of this report did have documented adrenal insufficiency and improved with steroid replacement therapy.

It is interesting to note that in all the cases of phenytoin-induced hypothermia in the literature, the patients had a

history of MR. Newberger and Blyth (2) cite a Dutch study of 60 patients with MR and seizure disorder in which the authors found a 20% incidence of mutations in the CYP2C9 gene responsible for phenytoin metabolism (9). The mean phenytoin dose required to achieve a therapeutic level was 37% lower in heterozygotes than in subjects with no mutation in this study. A genetic mutation could cause a predisposition to develop phenytoin toxicity at standard doses, but cannot explain either the occurrence of toxicity or the specific symptomatology seen in these cases.

CONCLUSIONS

Significant hypothermia may occur in the setting of phenytoin toxicity. Complex interactions between thermoregulation and phenytoin exist. Patients with a history of MR may be at greater risk for developing this condition. To our knowledge this is the first case report in which documented adrenal insufficiency may have played a role. Clinicians should be alerted to the potential for phenytoin toxicity to manifest with hypothermia and should obtain a core temperature measurement in all patients with elevated phenytoin levels and depressed mental status.

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