Phenytoin toxicity: A cause of reversible monoplegia[1]

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Phenytoin sodium (Dilantin), a frequently used anticonvulsant, has many well-recognized side effects. Of these, neurological ones are prominent and, when present, usually consist of ataxia, nystagmus, or dysarthria. Phenytoin toxicity in patients with previous strokes may present as a "re-stroke" syndrome. This paper reports a rare but recognizable complication in a patient in whom reversible monoplegia, a focal neurological deficit, developed during long-term phenytoin therapy for grand mal seizures.

Index terms: Neurologic manifestations • Paralysis • Phenytoin

Cleve Clin J Med 54:438–439, Sep/Oct 1987

Phenytoin sodium (Dilantin) is a frequently used anticonvulsant that has many well-recognized side effects. Of these, neurological ones are prominent and when present usually consist of ataxia, nystagmus, or dysarthria. It is not commonly appreciated that in patients with previous strokes phenytoin toxicity may present as a "re-stroke" syndrome. We have recently had the opportunity to evaluate a patient in whom reversible monoplegia, a focal neurological deficit, developed during long-term phenytoin therapy for grand mal seizures.

Case report

A 39-year-old black woman with an 8-year history of essential hypertension presented to our emergency department because she was unable to move her left leg secondary to dense monoplegia. Two years earlier, after a hypertensive intracerebral hemorrhage, left hemiplegia had developed and after recovery had left only a minor motor deficit involving the left leg. At the time of admission she said she "had her stroke back."

While recovering from her hemiparesis, she had grand mal seizures for which she received maintenance therapy with phenobarbital and phenytoin. When seen in follow-up after a few months of therapy, she complained of dizziness, headache, and staggering, but no motor deficits. Her serum phenytoin level was in the toxic range, so her physician decreased the dose from 300 mg/day to 100 mg at bedtime. With this reduction, her symptoms resolved except for an occasional headache.

For 21 months she did well until she had a generalized seizure, and her physician reinstituted a 300 mg/day schedule of phenytoin. Her serum phenytoin level at the time was 4.5 μg/mL (therapeutic range 10–20 μg/mL) and the possibility of noncompliance given the "low maintenance dose" was not entertained. On the third day of the higher dosage, the patient noted dizziness and unsteadiness in gait. With these symptoms she also noted that her left leg was becoming heavy. This heaviness progressed until 10 days later, two days before admission, when she was totally unable to move her left leg.

Physical examination at the time of her admission revealed an alert, oriented patient with slight slurring of her speech. Blood pressure was 150/100 mmHg, and the pulse rate was 78/min. Temperature was 98.8°F (37.1° C). Coarse nystagmus was present in all directions of gaze. Examination of the motor system disclosed dense monoplegia of the left lower extremity, exaggerated tendon reflexes,

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0891-1150/87/05/0438/02/$1.50/0

and positive Babinski sign on the left side. Hoover's sign for hysterical paralysis was negative. There was slightly diminished pinprick sensation on the left side, but there were no mental changes, papilledema, tremors, or facial asymmetry. Motor functions of the left upper extremity and on the right side were normal.

Laboratory investigations and specialized tests were performed. The complete blood count and WBC differential were normal, as were the serum electrolyte, blood urea nitrogen, creatinine, and glucose levels. Prothrombin and partial thromboplastin times were normal. Serologic tests for syphilis and antinuclear antibodies were negative; however her sedimentation rate (Wintrobe) was elevated to 26 mm/h (normal less than 20 mm/h).

Computed tomographic (CT) scans of the patient's head were interpreted as showing an area of "old hemorrhage in the right parietal area," but there was "no new hemorrhage." Electroencephalographic findings were reported as "consistent with underlying convulsive tendency without localizing or lateralizing features." The serum phenytoin level on admission was 38.1 μg/mL, a value clearly above the therapeutic range. Phenytoin therapy was discontinued and the patient continued to take phenobarbital (90 mg/day). About 48 hours after discontinuing phenytoin, the patient's condition improved. Her slurred speech resolved and the motor power of the left leg started to improve. However, the nystagmus and dizziness persisted.

Treatment was re-initiated at that time with 200 mg/day of phenytoin and clinical improvement ceased. Her nystagmus worsened and the motor functions of her left leg did not show any further improvement; she was still severely monoparetic. Consequently, the phenytoin was discontinued again after two days at the above dosages and after three further days she started to regain the motor tone of the flexor and extensor muscles of her left knee. Thereafter, daily improvement of her motor function continued along with progressive resolution of her nystagmus. She had no seizures while in the hospital. Multiple serum phenytoin levels were determined and serum half-life for phenytoin was found to be approximately 36 hours. After almost two weeks of hospitalization, the patient was discharged on a regimen of phenytoin 100 mg/day and phenobarbital 90 mg/day. One week after discharge, she was seen in our general medical clinic. She reported no seizures; the motor power of the left leg was markedly improved toward original baseline function, and there was no nystagmus. The serum phenytoin level at this time was 13.3 μg/dL, a therapeutic and tolerated level.

Discussion

This patient's presentation was very puzzling to her physicians at first, since these manifestations of drug toxicity are not common. A reversible "stroke syndrome" has been reported in six patients receiving phenytoin.[1-4] The predisposing feature of this interesting entity appears to be a prior neurological injury or deficit, which our patient had. The residual neurological impairment from the primary disease, before phenytoin exposure precipitates an exacerbation or recapitulation of the clinical process, may be quite minimal. In all reported cases, discontinuation of phenytoin therapy resulted in gradual and complete resolution of the focal neurological deficit.

In our patient Todd's paralysis was considered as a possible cause of her neurological deficit; however, the motor deficit did not immediately follow the seizure but began about 72 hours afterward and coincided with an increase in phenytoin dosage. A similar, reversible neurologic deficit can result from metabolic insults to the brain, including hypoglycemia, hypoxia, or hepatic or renal insufficiency; however, this patient did not have clinical or laboratory evidence of any of these derangements.

The pathophysiology of transient hemiparesis associated with phenytoin toxicity remains unknown. It may be related to compensatory supersensitivity of the inhibitory neurons utilizing gamma-aminobutyric acid (GABA) as a transmitter.[3,5]

This side effect of phenytoin therapy is being increasingly recognized. Clinicians, especially primary care physicians, need to be aware of it—more so, when they are confronted with a patient with a "re-stroke syndrome." Since discontinuation of phenytoin therapy in these patients results in complete resolution of the neurological deficits, we recommend that phenytoin therapy be discontinued in such patients and serum phenytoin levels measured before other more invasive and expensive procedures are pursued.

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