Pearls & Oy-sters:

Soft-tissue necrosis as a result of intravenous leakage of phenytoin

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CLINICAL PEARLS

1. Phenytoin leakage can cause potentially serious side effects ranging from mild edema to soft-tissue necrosis.
2. To avoid such events, one should consider using:
 - a. a dedicated IV catheter inserted in a large peripheral vein to infuse phenytoin;
 - b. administration rate ≤ 50 mg/min;
 - c. periodic flushing with saline after each bolus;
 - d. continuous monitoring for signs of extravasation, hypotension, and bradycardia.
3. The ease of administration, rapid onset of action, minimal morbidity, and IV solution compatibility are potential advantages of some of the second-line anticonvulsant agents, like valproate.

In the past 70 years, phenytoin (PHT) has been used in the management of seizures and remains, despite the advent of newer antiepileptic drugs,¹ one of the preferred long-acting antiepileptic drugs in the treatment of convulsive status epilepticus.² Injury due to PHT leakage may result in damage ranging from simple, mild phlebitis to severe lesions such as soft tissue necrosis.^{3,4} Up to 20% of IV administration of all drugs results in recognized episodes of extravasation.⁵ Nevertheless, few studies address the adverse events associated with the IV use of PHT.^{2,6} Factors believed to affect the extent of injury include the chemical properties of the drug, health status of the patient, and postextravasation care.³ We report the case of a 52-year-old woman who developed skin necrosis following IV administration of PHT as treatment of generalized convulsive status epilepticus (GCSE) and suggest some recommendations.

CASE REPORT A 52-year-old woman was admitted for presurgical evaluation of refractory epilepsy. During video-EEG monitoring, the patient developed GCSE lasting 18 minutes, not responsive to diazepam 10 mg IV. Undiluted 1,250 mg of PHT (20 mg/kg) was infused in the same peripheral venous line over 9 minutes, during which there were no

symptoms or physical signs of extravasation. Approximately 6 minutes after onset of PHT infusion, the seizure and electrographic status epilepticus ceased. Within 2 hours, the patient was alert and started to complain of a burning sensation in the area of infusion. An erythematous lesion could be seen in that region. Four hours later, a new examination disclosed a large area of swelling and hyperemia with a central area of skin necrosis with a typical black coloration (figure, A). Radial and ulnar arterial pulses were preserved. She had mild pain at the lesion site. Tissue and blood samples were collected for culture, which turned out to be negative. Other laboratory examination results were also normal. A plastic surgery consultation suggested local debridement as the appropriate treatment (figure, B).

DISCUSSION Along with phenobarbital, PHT remains one of the most widely used antiepileptic drugs in the acute treatment of GCSE.^{1,2} The introduction of oral PHT in 1938 and its subsequent parenteral formulation represented a significant advance in anticonvulsant therapy.

PHT is a highly alkaline (pH 12), poorly water soluble compound. Because of the risk of systemic adverse effects, like hypotension and cardiac arrhythmias, administration is usually carried out at no more than 50 mg/min. Mixing PHT with 5% dextrose may result in lack of solubility and precipitation, but it can be dissolved in no more than 20 mg/mL in normal saline without such problems.² The parenteral formulation of IV PHT produces pain at the injection site and is irritating to soft tissue, sometimes resulting in phlebitis. In order to reduce this complication, injection of sterile saline is recommended during and after the administration of IV PHT.²

Local complications like edema, phlebitis, tissue necrosis, and the “purple glove” syndrome⁷ may occur. In a prospective study that assessed the adverse side effects following the use of IV PHT,⁴ 6 patients (27%) experienced one or more side effects, includ-

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Figure Lesion evolution during healing period

(A) Four hours after phenytoin infusion: erythema, edema, and central soft tissue necrosis.
(B) Two weeks after infusion: signs of wound healing with adequate scar tissue.

ing extravasation of the drug, hypotension, and cardiac arrhythmia.

PHT can be associated with potentially serious side effects ranging from mild edema to soft-tissue necrosis.⁸ Therefore, one should follow patients closely after IV PHT infusion and consider the following recommendations: 1) use a dedicated IV catheter in a large peripheral vein to infuse phenytoin; 2) administration must be carried out at no more than 50 mg/min (in children and elderly no more than 25 mg/min); 3) periodically flush the IV access with saline bolus during the PHT infusion; 4) systematically monitor for signs of extravasation, hypotension, and bradycardia; 5) closely follow neurologic and circulatory status of the patient.

Fosphenytoin is an alternative to PHT, as it can be administered more quickly and safely.⁹ Likewise, other newer antiepileptic drugs are emerging as potential options for treatment of GCSE.¹ IV valproate

has several potential advantages: it can be easily administered at faster infusion rates, is effective in all age groups, has a rapid onset of action, has proven broad-spectrum efficacy, and has minimal side effects, all of which may warrant its inclusion in status epilepticus treatment protocols. Levetiracetam, despite somewhat mixed results in animal studies, has been reported to be successful in case reports in human GCSE.¹⁰ These preliminary reports suggest a possible role of levetiracetam in the initial management of status epilepticus, especially due to its ease of use, administration, and limited side effects. Recently, IV lacosamide was reported as a successful treatment option for nonconvulsive status epilepticus.¹¹ Prospective randomized trials with the new anticonvulsants are encouraged.

DISCLOSURE

Dr. Twardowsky reports no disclosures. Dr. De Paola serves as Editor of the *Journal of Epilepsy and Clinical Neurophysiology*. Dr. Germiniani, Dr. Werneck, and Dr. Silvado report no disclosures.

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