

Purple Glove Syndrome

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PA-PSRS has received several reports regarding "purple glove syndrome," an adverse drug reaction related to intravenous administration of phenytoin (DILANTIN). To address this topic, PA-PSRS invited Patrick J. McDonnell, PharmD, to submit this article. Dr. McDonnell specializes in drug safety and adverse drug reactions and has lectured and written extensively on these issues.

—John R. Clarke, M.D., Editor

An 82-year-old female with a history of seizure was unable to continue oral therapy of phenytoin due to new onset of seizure activity, so she was prescribed phenytoin 100 mg IV q8h. The phenytoin was infused via a #22-gauge catheter in her right hand, and when the nurse left the room, the patient dislodged the phenytoin infusion. The patient's right hand was cool with a purple mottling spreading from the IV site. Her attending physician was notified, and warm compresses with elevation were applied to the area. Plastic surgery was consulted, and Doppler studies revealed adequate perfusion. The patient was diagnosed with "purple glove syndrome" from phenytoin. Within three days, symptoms appeared to be improving with decreased edema of the right hand and less mottling. No necrosis was noted.

Phenytoin (**DILANTIN**), a broad spectrum anticonvulsant, has been widely administered parenterally for the treatment of seizures for more than 40 years. It is used as a first-line therapy for status epilepticus. Intravenous (IV) phenytoin is employed in emergency departments and neurological units for patients with active seizure disorders or who are unable to receive oral medication.

Adverse reactions to phenytoin are not uncommon in regards to phenytoin toxicity, due to phenytoin's narrow therapeutic index and pharmacokinetics; however, the adverse drug reaction known as purple glove syndrome (PGS) (see the PA-PSRS case report above), seems to be related exclusively to the IV administration of phenytoin.

PGS gets its name from the characteristic bluish discoloration of the skin, accompanied by pain and edema distal to the site of intravenous administration of phenytoin. Generally, PGS occurs in three stages:^{1,4}

1. A pale blue or dark purple discoloration appears around the intravenous insertion site 2 to 12 hours after the administration of the drug.
2. Progression occurs during the next 12 to 16 hours as developing edema and continued discoloration spread around all sides of the fingers, hand and forearm, hence the term "purple glove."
3. Healing is the last stage as the discoloration recedes, starting from the periphery and moving toward the original site of injury. The majority of reported cases resolve without incident, but a few cases resulting in necrosis have been reported.

The mechanism for PGS is not totally understood but seems to be related to the reaction of the interstitial tissue to extravasation of the highly alkaline pH of phenytoin injection. However, not all cases of PGS are preceded by typical or blatant extravasation, and this varying reaction is related to the formulation of phenytoin injection.

Phenytoin injection is poorly soluble in water. Several vehicles must be employed to improve solubility to allow the drug to be administered parenterally. Phenytoin injection is available as a solution that contains 50 mg of phenytoin sodium per milliliter in a vehicle of 40% propylene glycol and 10% ethanol; this solution is then adjusted to a pH of 12 with sodium hydroxide. PGS seems to occur not directly

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Purple Glove Syndrome (Continued)

from phenytoin, but from these additives. PGS occurs without blatant or visible extravasation for several reasons, including the following:¹

- The highly alkaline phenytoin solution may induce vasoconstriction and thrombosis, which then result in an occult leakage of solution into the interstitial space.
- Mixing this alkaline solution with blood of a more neutral pH may result in precipitation of phenytoin that can lead to vascular and IV catheter obstruction.
- The solution's alkalinity may also result in the breakdown of endothelial intercellular junctions allowing phenytoin to seep into the skin's interstitial spaces.
- The IV catheter insertion may cause a microtear in the vessel wall, allowing a small amount of phenytoin to infiltrate the soft tissue without apparent extravasation. Such tears are more likely during catheter insertions on elderly patients.

The actual incidence of PGS is unknown. More attention in the late 1990s focused on PGS with the introduction of fosphenytoin, a pro-drug of phenytoin that is highly water soluble at a neutral pH (blood pH) and is delivered in a vehicle less caustic than phenytoin. One study placed the incidence of PGS at 5.9% (i.e., 9 of 152 patients who received IV phenytoin during the study) and promoted the use of fosphenytoin to prevent PGS.¹ Another study found that PGS incidence with IV administration of phenytoin was 1.6%, with the cases being mild and unremarkable with no effect on increase in hospital length of stay.²

Regardless of the incidence, increased awareness of this reaction by prescribers, pharmacists, nurses or others who administer IV phenytoin is necessary.

To reduce the likelihood of PGS, staff education and drug information material about phenytoin should include the following:³

- Phenytoin, whether given by IV push or IV infusion, should never be administered at a rate greater than 50 mg/min; some advocate a rate of infusion of 20 mg/min for the elderly or for patients with poor IV access.

- Phenytoin, if diluted in IV fluids, can only be diluted in 0.9% saline (NSS) and should be mixed immediately prior to administration to prevent precipitation. Bacterostatic isotonic saline should not be used, as preservatives can lead to precipitation. Any phenytoin admixture more than four hours old should be discarded.
- Dextrose solutions and lactated ringers solution cannot be used with IV phenytoin due to the potential for precipitation.
- Smaller hand veins should be avoided as IV administration points.
- 20-gauge catheters or larger should be utilized along with a 0.22 micron filter.
- Careful monitoring of the site during and post infusion should be employed.

If pain, discoloration and/or edema develop despite these precautions, the following treatment plans are suggested to lessen the severity of PGS:³

- Discontinuing IV administration of phenytoin
- Applying gentle, dry, warm heat to the area to relieve pain and help to redistribute phenytoin within the soft tissue; moist heat is not recommended as it may contribute to skin breakdown or maceration
- Elevating extremities to aid in symptom relief and reduce edema
- Employing pain assessment and management
- Continuing neurovascular assessment of the area and documenting pain, skin condition and limb movement
- Avoiding use of cold compresses, as this leads to vasoconstriction and impaired resolution and healing of PGS

Increased awareness of PGS, precautionary IV administration of phenytoin, and prompt action if PGS

Purple Glove Syndrome (Continued)

does occur can limit the progression of soft tissue damage seen with this adverse drug reaction.

Notes

1. O'Brien TJ, Cascino GD, So EL, et al. Incidence and clinical consequences of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology* 1998 Oct;51(4):1034-9.
2. Burneo JG, Anandan JV, Barkley GL. A prospective study of

the incidence of purple glove syndrome. *Epilepsia* 2001 Sep;42(9):1156-9.

3. Meek PD, Davis SN, Gidal M, et al. Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. *Arch Intern Med* 1999 Dec;159(22):2639-44.

4. Spengler RF, Arrowsmith JB, Kilarski DJ, et al. Severe soft-tissue injury following the intravenous infusion of phenytoin. *Arch Intern Med* 1988 Jun;148(6):1329-33.

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