Phenytoin-Induced Purple Glove Syndrome: A Case Report and Review of the Literature

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Case Report

Phenytoin-Induced Purple Glove Syndrome: A Case Report and Review of the Literature

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ABSTRACT
Objective: To present a case report and literature review of phenytoin-induced purple glove syndrome (PGS).
Case summary: A 54-year-old African American male presented to our hospital’s emergency department (ED) following a seizure episode, cardiac arrest, and loss of consciousness. On arrival to the ED, the patient’s total phenytoin level was subtherapeutic at 4.1 mcg/mL and his corrected total phenytoin level was subtherapeutic at 5.1 mcg/mL. In the ED, the patient received a loading dose of intravenous (IV) phenytoin 1,000 mg once via the left cephalic vein, at a rate of 50 mg/min, and was admitted to the medicine service. A day following IV phenytoin administration, a nurse noticed an IV fluid infiltration on the skin tissue around the left cephalic vein. The area appeared dark blue and purple in color, swollen, erythematous, and warm to touch. An ultrasound of the left upper extremity was performed and revealed subcutaneous fluid collection without evidence of thrombosis.
Discussion: The Naranjo Adverse Drug Reaction Probability Scale assigned a score of 7, indicating phenytoin as the probable cause of purple glove syndrome (PGS). The patient’s PGS was managed with a combination of dry dressing material, left forearm elevation, collagenase topical cream, 0.1% IV bupivacaine, and IV fentanyl. The patient’s injury was resolving at the time of discharge to a rehabilitation facility.
Conclusion: PGS is a rare complication of IV phenytoin therapy. The risk of PGS for this patient may have been abated by decreasing the phenytoin infusion rate from 50 mg/min to less than 25 mg/min.

Key Words—adverse reactions, arm injuries, extravasation, phenytoin, seizures

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Purple glove syndrome (PGS) is a rare complication of intravenous (IV) phenytoin administration that is characterized by delayed soft tissue injury of the skin adjacent to the site of IV phenytoin infusion. PGS may occur with or without extravasation of IV phenytoin. The clinical manifestation of PGS includes pain, edema, and purple-blue discoloration of skin tissue adjacent to the site of IV phenytoin infusion. Clinically, PGS development encompasses 3 stages. During the first stage, which occurs within 2 to 12 hours after infusion of IV phenytoin, a dark purple-bluish discoloration of the skin appears around the site of IV phenytoin infusion. In the second stage, which occurs in the next 12 to 16 hours, edema develops and there is progression of the dark purple-bluish discoloration around the skin...
surrounding the infusion site. During the final stages of PGS, healing occurs with resolution of edema and recession of skin tissue discoloration. PGS has been described as being painful through all of its stages. On very rare occasions, PGS may progress to necrosis, ischemia, vascular compression, or compartment syndrome, which may require surgical interventions such as fasciotomy, skin grafting, or rarely amputation. PGS has been found to prolong a patient’s hospital length of stay.

**CASE REPORT**

A 54-year-old African American male with a history of paraplegia secondary to gunshot wound 10 years prior, nephrectomy, and seizures was admitted to the hospital after experiencing cardiac arrest and seizure episode. He was last observed playing wheelchair basketball. As he was playing, he fell backwards, slipped off his wheelchair, and hit his head on the floor. He had no immediate complaint and continued to play for another hour. He soon began to feel nauseated, dizzy, and short of breath. The patient quickly developed seizure activity and became unresponsive. Two bystanders provided cardiopulmonary resuscitation and activated the emergency response system. The Emergency Medical Services team arrived and found the patient to be in asystole. Advanced Cardiovascular Life Support (ACLS) protocol was initiated, and the patient progressed from asystole to ventricular fibrillation to pulseless electrical activity and then sinus tachycardia prior to presenting to the emergency department (ED). As part of the ACLS protocol, the patient received epinephrine 1 mg IV 4 times, electrical cardioversion (shock) 4 times, atropine 1 mg IV 4 times, amiodarone 300 mg IV once, and one ampule of sodium bicarbonate once, prior to presenting to the ED.

On physical examination, his vital signs were as follows: temperature 30.8°C, heart rate 88 bpm, systolic blood pressure 92 mm Hg, diastolic blood pressure 59 mm Hg, respiratory rate 20 rpm on mechanical ventilation, and oxygen saturation of 95%. There was muscle fasciculation with shivering. The patient’s pupils were nonreactive, and he was unreactive to pain. Cardiovascular exam revealed regular rate and rhythm with no murmurs, rubs, or gallops. Chest was clear to auscultation. No cyanosis, clubbing, or edema was noted on examination of his extremities. The complete metabolic panel results were as follows: sodium 142 mEq/L, potassium 3.5 mEq/L, chloride 105 mEq/L, bicarbonate 18 mEq/L, blood urea nitrogen (BUN) 25 mg/dL, serum creatinine 1.65 mg/dL, serum glucose 250 mg/dL, calcium 8.8 mg/dL, albumin 3.5 gm/dL, aspartate aminotransferase (AST) 147 U/L, alanine aminotransferase (ALT) 525 U/L, and alkaline phosphatase 100 U/L. Complete blood count results were as follows: white blood cell count 6.1 x 10^3/μL, hemoglobin 12.8 g/dL, hematocrit 39.4%, and platelet 136 x 10^9/L, PT 15.1 seconds, INR 1.3, and PTT 27.6 seconds. Cardiac enzyme was significant for CK-MB 7.3 ng/mL and cardiac troponin 0.03 ng/mL.

Therapeutic drug monitoring results were as follows: Total phenytoin level was subtherapeutic at 4.1 mcg/mL (total phenytoin therapeutic level = 10 to 20 mcg/mL) and corrected total phenytoin level (correcting for albumin of 3.5 g/dL) was still subtherapeutic at 5.1 mcg/mL. A loading dose of IV phenytoin 1,000 mg was given to patient once in the ED at a rate of 50 mg/min. The needle gauge size used for phenytoin administration is unknown and was not documented on the patient’s chart. Subsequent phenytoin administration was given as phenytoin 100 mg every 8 hours via nasogastric tube.

On the second day of hospital admission, approximately 12 hours after the infusion of IV phenytoin through the left cephalic vein of the forearm, the nurse noted left forearm swelling and skin discoloration (dark blue and purple in color) that she assumed was a benign local injection site reaction. The nurse proceeded with hanging IV amiodarone. Shortly after, IV fluid began seeping out of the left forearm. Upon noticing the left arm swelling with IV fluid seeping out, the nurse discontinued the amiodarone drip and switched to an enteral dosage form to avoid further injury to the left arm skin above the left cephalic vein. An initial physical examination of the skin region covering the left forearm where the IV infiltrate was seen noted subsequent hematoma with progressive swelling and dark blue and purplish skin discoloration. An ultrasound of the left upper extremity, performed on the same day, revealed subcutaneous fluid collection without evidence of venous thrombosis. A repeat physical examination of the left forearm, performed about 60 hours from the onset of the injury, revealed presence of hematoma, subsiding swelling and erythema, blisters, dark skin discoloration (dark blue/purplish in color), and surrounding necrotic tissue. Figure 1 depicts an intermediate stage between stages 2 and 3 of PGS. The edema has subsided and erythema has lessened; however some areas of dark blue and purple discoloration still exist with some blisters seen around the open wound.
General surgery was consulted on the day of onset of injury; after evaluating the injury, they referred care of the patient’s injury to the wound care team. The wound care team used a combination of dry dressing material and left forearm elevation to reduce edema. Collagenase topical cream was also applied in the injured area to promote healing of the left forearm injury, and 0.1% IV bupivacaine and IV fentanyl (2 mcg/mL) at a rate of 1 to 2 mL/h were administered to alleviate pain. The patient’s injury was healing (subsiding swelling and receding of the area of discoloration) by the time he was discharged to an external rehabilitation facility, 17 days after the injury was first observed on his left forearm. The Naranjo Adverse Drug Reaction Probability Scale assigned a score of 7, indicating phenytoin as the probable cause of PGS in this case (see Table 1).

DISCUSSION

PGS is a rare complication of IV phenytoin therapy. The incidence of PGS among patients receiving IV phenytoin ranges from 1.7% to 5.9%. These data come from a retrospective and a prospective analysis of patients receiving consecutive IV phenytoin at 2 institutions. Post hoc ratio estimation of PGS incidence was conducted by Burneo et al using information from their study along with the O’Brien study to reveal that the estimated population incidence of PGS lies between 0% and 4.1% among patients receiving IV phenytoin.

The mechanism underlying the development of PGS is not well understood. Several theories have been proposed. It was originally thought that PGS occurred due to extravasation of the highly alkaline IV phenytoin solution; however, recent data have shown that PGS can occur with or without clinically apparent extravasation. Most recently, Yoshikawa et al reported a case of PGS following oral administration of phenytoin that provides supporting evidence that PGS may occur with or without phenytoin extravasation. This case of PGS following oral phenytoin was observed in a patient with supratherapeutic serum levels of phenytoin. This has raised the question as to whether phenytoin itself, irrespective of route of administration, may induce PGS in patients due to phenytoin doses and serum levels that are higher than recommended therapeutic doses or levels.

The extravasation theory suggests that the highly alkaline IV phenytoin solution (pH = 12) contributes to the development of PGS when it infiltrates extraneously into surrounding tissues. Phenytoin is a weak organic acid and is very insoluble. Sodium hydroxide is added to IV phenytoin solution to increase its alkalinity. Propylene glycol and ethanol are also added to IV phenytoin solution to increase its solubility. These 3 pharmaceutical additives (sodium hydroxide, propylene glycol, and ethanol) are well-known soft tissue irritants; when they are infused extraneously, they may produce PGS. Extravasation of phenytoin may also occur due to a microtorn of the vein during the IV cannulation procedure.

Theories supporting the development of PGS without extravasation place emphasis on the pharmacologic properties of phenytoin and its anatomic and physiologic interactions. These theories emphasize phenytoin-related vasoconstriction and precipitation as the triggering phenomenon leading to the development of PGS. It has been proposed that highly alkaline phenytoin solution may induce vasoconstriction, which results in the leakage of the phenytoin solution into surrounding interstitial soft tissue spaces. The phenytoin-induced vasoconstriction is usually followed by damage of vascular endothelial integrity, which promotes further leakage of phenytoin solution into adjacent interstitial soft tissue spaces. It has also been proposed that the mixing of the highly alkaline IV phenytoin solution with the more neutral pH of blood may produce precipitation of phenytoin that may obstruct the vein and lead to phenytoin back-up and leakage into soft tissue interstitial spaces and development of PGS.

The development of edema during PGS is attributable to the highly protein-bound phenytoin in the interstitial spaces increasing the interstitial oncotic pressure, which creates a pressure gradient that facilitates the accumulation of fluids (third-spacing) in the soft tissue adjacent to the IV phenytoin infusion site.

Established risk factors for PGS include age, indication for phenytoin usage, phenytoin dose, and number of IV phenytoin doses received. Generally
Purple Glove Syndrome

Table 1. Assessing phenytoin-induced PGS using Naranjo Adverse Drug Reaction Probability Scale

<table>
<thead>
<tr>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
<th>Phenytoin score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>+2</td>
</tr>
<tr>
<td>Did the adverse reaction improve when the drug was discontinued or specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>Did the adverse event reappear when the drug was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>+2</td>
</tr>
<tr>
<td>Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the drug detected in blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

patients who are 60 years old and older, who receive phenytoin for acute seizure indications, or who receive large doses and multiple doses of IV phenytoin are more predisposed to developing PGS.1 Along with the more established risk factors for PGS, Spengler et al8 performed a case-control study that revealed that women, patients receiving high phenytoin infusion rates (>25 mg/min), and the use of IV catheter bore sizes smaller than 20 gauge (20-G) (ie, smaller bore diameter and higher gauge [>20-G] value) are associated with an increased risk of PGS. It is important to note that there is conflicting evidence with regard to the role of IV catheter bore size as a risk factor for PGS. Spengler et al8 reported higher risk of PGS with IV catheter bore sizes smaller than 20-G (smaller bore diameter and higher gauge value), and O’Brien et al1 reported the use of IV catheter bore sizes greater than 20-G (larger bore diameter and lower gauge value) in most of the patients (89%) developing PGS in his study. Another less empirically supported risk factor that predisposes patients to PGS is the presence of conditions that weaken vascular and skin integrity.1

PGS may be prevented by adjusting modifiable established risk factors that are associated with the development of PGS, namely the use of higher phenytoin infusion rates and the administration of multiple doses of IV phenytoin. It is prudent to use IV phenytoin infusion rates less than 25 mg/min and to convert patients to oral phenytoin, when appropriate, to prevent the occurrence of PGS.

PGS usually resolves with nonpharmacologic therapy after the discontinuation of IV phenytoin, consisting of elevation of limb, application of dry gentle heat, and warm compresses.1–3 Anecdotal reports have documented beneficial outcomes with the use of a low concentration of IV 0.1% bupivacaine and fentanyl (2 mcg/mL) to localize and alleviate pain.10 On very rare occasions, PGS may progress to necrosis, ischemia, vascular compression, or compartment syndrome, which may require surgical interventions such as fasciotomy, skin grafting, or amputation.1,2

CASE SUMMARY

The patient improved following the use of a combination of dry dressing material, left forearm elevation, collagenase topical cream, 0.1% IV bupivacaine, and IV fentanyl. The patient’s injury was healing (subsiding swelling and receding of the area of discoloration) by the time he was discharged to an external cardiac and neurologic rehabilitation facility, 17 days after the injury was first observed on his left forearm. The modifiable risk factor of reducing the phenytoin infusion from 50 mg/min to less than 25 mg/min may have prevented PGS in this patient.
REFERENCES


