A 60-year-old African-American man presented to the emergency department with malaise, fever, and mild shortness of breath. Following initial evaluation and application of supplemental oxygen, the patient was admitted to a step-down unit. Seventy-two hours following admission, his respiratory status declined, and he was transferred to the medical ICU.

Following this transfer, endotracheal intubation, and initiation of positive-pressure ventilation with a fraction of inspired oxygen of 0.6 and positive end-expiratory pressure of 10 cm H₂O, the patient was oxygenating poorly and was increasingly agitated. To control agitation and minimize peak inspiratory pressures, the patient was sedated with lorazepam by bolus and infusion dosing. After additional bolus doses of lorazepam and escalation of the infusion rate to produce deep sedation, he was paralyzed with cis-atracurium besylate to facilitate inverse ratio ventilation. Other medications administered included trimethoprim-sulfamethoxazole, prednisone, sulfate, flutamide, glipizide, and acyclovir.

**Physical Examination**

The patient’s temperature was 37.2°C (99.0°F); respirations, 18 breaths/min (ventilator rate); heart rate, 104 beats/min; and BP, 110/56 mm Hg. Lung auscultation revealed adequate air movement bilaterally, upper airway rhonchi that cleared with endotracheal suctioning, and scattered expiratory wheezing. The abdomen was soft, and tenderness could not be assessed in the presence of neuromuscular blockade; however, bowel sounds were normal. Full neurologic assessment could not be performed due to the presence of sedation and neuromuscular blockade.

**Laboratory Findings**

Laboratory findings included the following: WBC count, 21,000 cells/µL; hemoglobin, 10.6 g/dL; hematocrit, 33%; Na⁺, 136 mEq/L; K⁺, 5.0 mEq/L; Cl⁻, 106 mEq/L; CO₂, 18 mEq/L; BUN, 35 mg/dL; creatinine 0.8 mg/dL; and glucose, 296 mg/dL. Serum lactic acid level was 25.8 mg/dL, with serum osmolality of 321 mOsm/L. The osmolar gap was 21 mOsm/L. Arterial blood gas measurements on fraction of inspired oxygen of 0.6 were: pH 7.26; Pco₂, 35 mm Hg; and Po₂, 126 mm Hg. The osmolar gap was determined by the following formula:

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\text{Osmolar gap} = \text{measured serum osmolality} - \text{calculated serum osmolality}
\]

Calculated serum osmolality = \(2(\text{Na}^+) + \text{Glu}/18 + \frac{\text{BUN}}{3}\)

Following 5 days of therapy with the escalating lorazepam infusion, the patient developed an osmolar gap metabolic acidosis.

What was the cause of the osmolar gap metabolic acidosis?
Diagnosis: Propylene glycol toxicity caused by escalating lorazepam infusion.

Lorazepam is an intermediate-acting benzodiazepine commonly utilized in sedation of critically ill adult patients. The drug is generally well tolerated, particularly in patients who are hemodynamically stable and receiving positive-pressure ventilation. However, with moderate or escalating doses of this agent, the drug solvent, propylene glycol (PG), can cause toxicity.

PG, 1,2-propanediol, is a colorless, odorless fluid that is used commonly as a solvent for many IV drugs. Other agents with PG as the drug vehicle include etomidate, phenytoin, diazepam, digoxin, hydralazine, esmolol, chlorodiazepoxide, multivitamins, nitroglycerin, pentobarbital sodium, phenobarbital sodium, and trimethoprim-sulfamethoxazole. PG also can be absorbed through skin or mucous membranes from topical preparations for burns.

After its absorption, the kidneys eliminate 45% of the PG, with the remainder metabolized by the liver to lactic acid, pyruvic acid, or acetone. As a result, patients with impaired liver and/or kidney function are at increased risk for developing PG toxicity. The mean elimination half-life of PG is 2.3 ± 0.7 h. Serum levels of PG > 18 mg/dL can be toxic. PG toxicity has been associated with intravascular hemolysis, CNS depression, seizures, cardiac arrhythmias, and respiratory arrest. PG toxicity can be the cause of hyperosmolality and metabolic (lactic) acidosis with an osmolar gap. The differential diagnosis of an increased osmolar gap should include toxic ingestions, such as methanol or antifreeze (ethylene glycol), and concurrent medications. Following interruption of an IV infusion, serum PG concentrations decrease rapidly and correlate with resolution of clinical signs of toxicity.

Our patient’s lorazepam infusion was mixed in a 1:1 concentration: 1 mg of lorazepam to 1 mL of solution for infusion. Each milliliter of the base solution dispensed from the vial (2 mg lorazepam/mL) contains 0.8 mL (830 mg) of PG as the drug vehicle. In the concentration utilized for infusion, each milliliter of the infusion contained 0.4 mL (415 mg) of PG. With the lorazepam infusion at a rate of 6 mL/6 mg/h, the patient was receiving 2.4 mL (2.49 g) of PG per hour. Over the entire course of therapy with lorazepam infusion, the total lorazepam dose was 1,302 mg. The total PG load was 540 g. As a food additive, the maximum daily permissible intake of PG is 25 mg/kg or 1,975 mg/d for an individual weighing 75 kg.

As a result, our patient developed an osmolar gap metabolic (lactic) acidosis after 5 days of lorazepam infusion at 6 mg/h. Other possible sources of tissue hypoxia that could account for a lactic acidosis were excluded. The serum PG level of 78 mg/dL obtained from the patient when the lorazepam was discontinued confirmed the clinical diagnosis. The patient’s simultaneously obtained serum pyruvate level was also elevated at 1.01 mg/dL (normal, 0.3 to 0.7 mg/dL). The lorazepam was discontinued, and the lactic acid concentration and anion and osmolar gaps returned to normal within 72 h.

Clinical Pearls

1. PG toxicity is manifested by an anion gap metabolic acidosis with associated osmolar gap, as it is metabolized to lactic acid, pyruvate, and acetone.
2. Appropriate intervention should begin immediately for PG toxicity; it should not be delayed pending serum PG levels.
3. Appropriate intervention for PG toxicity includes replacement therapy to decrease total PG load. Replacement therapy may include midazolam, propofol, narcotics, or a long-acting benzodiazepine such as diazepam.
4. PG toxicity can occur with any IV agent that contains it as a diluent, such as etomidate, phenytoin, digoxin, hydralazine, esmolol, chlorodiazepoxide, and nitroglycerine, as well as with topical treatment, such as silver sulfadine cream for burn therapy.

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Suggested Readings