

CASE REPORT

Severe Lactic Acidosis After an Iatrogenic Propylene Glycol Overdose

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Propylene glycol is a diluent found in many intravenous and oral drugs, including phenytoin, diazepam, and lorazepam. Propylene glycol is eliminated from the body by oxidation through alcohol dehydrogenase to form lactic acid. Under normal conditions, the body converts lactate to pyruvate and metabolizes pyruvate through the Krebs cycle. Lactic acidosis has occurred in patients, often those with renal dysfunction, who were receiving prolonged infusions of drugs that contain propylene glycol as a diluent. We describe a 50-year-old man who experienced severe lactic acidosis after receiving an accidental overdose of lorazepam, which contains propylene glycol. The patient was acutely intoxicated, with a serum ethanol concentration of 406 mg/dl. He had choked on a large piece of meat and subsequently experienced pulseless electrical activity with ventricular fibrillation cardiac arrest. He was brought to the emergency department; within 2 hours, he was admitted to the intensive care unit for initiation of the hypothermia protocol. The patient began to experience generalized tonic-clonic seizures 12 hours later, which resolved after several boluses of lorazepam. A lorazepam infusion was started; however, it was inadvertently administered at a rate of 2 mg/minute instead of the standard rate of 2 mg/hour. Ten hours later, the administration error was recognized and the infusion stopped. The patient's peak propylene glycol level was 659 mg/dl, pH 6.9, serum bicarbonate level 5 mEq/L, and lactate level 18.6 mmol/L. Fomepizole was started the next day and was continued until hospital day 3. Continuous renal replacement therapy was started and then replaced with continuous venovenous hemofiltration (CVVH) for the remainder of the hospital stay. The patient's acidosis resolved by day 3, when his propylene glycol level had decreased to 45 mg/dl. Fomepizole was discontinued, but the patient's prognosis was poor (anoxic brain injury); thus care was withdrawn and the patient died. Although the patient's outcome was death, his lactic acidosis was treated successfully with fomepizole and CVVH. Clinicians should be aware that an iatrogenic overdose of lorazepam may result in severe propylene glycol toxicity, which may be treated with fomepizole and CVVH.

Key Words: propylene glycol, lorazepam, iatrogenic overdose, severe lactic acidosis, critical care, fomepizole.

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Propylene glycol is a diluent found in many intravenous and oral drugs, including phenytoin, diazepam, and lorazepam. Propylene glycol is eliminated from the body by oxidation through alcohol dehydrogenase to form lactic acid (Figure 1). Under normal conditions, the body

converts lactate to pyruvate and metabolizes the pyruvate through the Krebs cycle. Several reports have described lactic acidosis that occurred in patients in intensive care settings who received extended infusions of drugs that contained propylene glycol as a diluent.^{1,2} These

cases were due to prolonged infusions of therapeutic doses, often in patients with renal dysfunction. We describe a patient who experienced lactic acidosis after receiving an iatrogenic overdose of lorazepam, which contains propylene glycol.

Case Report

A 50-year-old man with a history of alcohol and cocaine abuse was brought to the emergency department after choking on a large piece of meat and subsequently experiencing pulseless electrical activity with ventricular fibrillation cardiac arrest. Within 2 hours of arriving, the patient was transferred to the intensive care unit for initiation of the hospital's hypothermia protocol; cooling was continued for 24 hours. On admission, the patient was acutely intoxicated, with a serum ethanol concentration of 406 mg/dl.

Approximately 12 hours after admission, the patient developed generalized tonic-clonic seizures that resolved after several boluses of lorazepam. The seizures were presumed to be due to anoxic brain injury from prolonged hypoxia. A lorazepam infusion was started; however, it was inadvertently administered at a rate of 2 mg/minute instead of the standard rate of 2 mg/hour. Over the next few hours, the patient became acidemic (pH 6.9) and hypotensive. A norepinephrine infusion was started, and his mean arterial pressure was 60–65 mm Hg.

Ten hours after the lorazepam infusion was started, the administration error was recognized and the infusion stopped. The patient's total dose of lorazepam was approximately 1.2 g. Three hours later, the patient's arterial pH was 6.9 and serum bicarbonate level 5 mEq/L (normal range 22–32 mEq/L); a sodium bicarbonate infusion was started. His peak serum propylene glycol concentration was 659 mg/dl, analyzed by high-performance liquid chromatography, and his serum creatinine and lactate concentrations were 0.8 mg/dl (0.4–1.2 mg/dl) and 14.6 mmol/L (0.5–2.2 mmol/L), respectively. The time course of the patient's

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serum propylene glycol and lactate levels are shown in Figure 2.

Four hours after stopping the lorazepam infusion, intravenous fomepizole was administered as follows: 15-mg/kg bolus followed by 10 mg/kg every 12 hours for one dose, 10 mg/kg every 6 hours for four doses, and then 15 mg/kg every 6 hours during renal replacement therapy until acidosis resolved and his propylene glycol concentration was 45 mg/dl. Continuous renal replacement therapy was initiated 18 hours after the lorazepam infusion had been stopped. This was replaced 18 hours later when the patient's hypotension had resolved, with continuous venovenous hemofiltration, which was continued until the patient's death. The patient's serum creatinine concentration began to rise 42 hours into his hospitalization. He was diagnosed with acute tubulonecrosis and renal failure. At 70 hours (hospital day 3), the patient's acidosis had resolved, his serum propylene glycol concentration

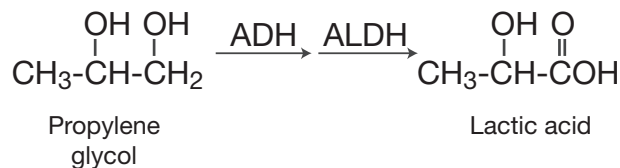


Figure 1. Metabolism of propylene glycol to lactic acid. ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase.

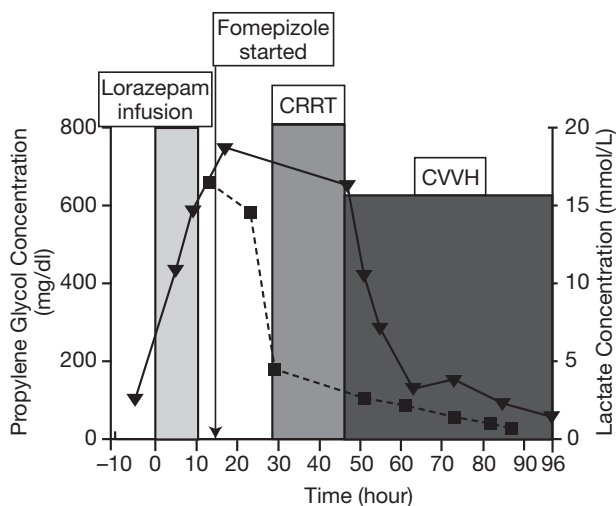


Figure 2. Time course of the patient's serum propylene glycol and lactate concentrations in relation to the 10-hour infusion of lorazepam 2 mg/minute and the treatments administered. CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration.

was 45 mg/dl, and fomepizole was discontinued. Unfortunately, the patient did not recover from renal failure and had suffered hypoxic brain injury from his initial cardiac arrest. With the family's consent, the patient was extubated on hospital day 12 and died within the next few minutes.

Discussion

Propylene glycol toxicity is well described in the literature after prolonged infusions of drugs containing this diluent, especially in patients with renal failure.³ Our patient developed severe lactic acidosis from propylene glycol toxicity after a 10-hour infusion of lorazepam 1.2 g. His serum propylene glycol concentration was among the highest, to our knowledge, ever reported, and his lactic acidosis was temporally related to the propylene glycol overdose. Other possible causes of lactic acidosis in our patient seem less likely. For example, although the patient had seizures, he did not continue to seize after an initial bolus of lorazepam, and prolonged, severe lactic acidosis is not consistent with limited seizure activity. Alcoholic ketoacidosis may result in elevated lactate levels. Although this patient was a chronic alcoholic, he received intravenous dextrose during his hospital stay, which should have prevented ketoacidosis. Renal failure can result in high serum concentrations of uncleared acids. However, this patient had no evidence of renal failure, indicated by his initial serum creatinine concentration of 0.8 mg/dl. Cocaine toxicity may produce an elevated lactate concentration, but the patient did not have evidence of cocaine toxicity when he arrived at the emergency department. In addition, the time course is not consistent with cocaine toxicity producing the acidosis, as symptoms usually develop almost immediately after ingestion or inhalation. The patient's elevated propylene glycol level is much more likely to be the cause of his lactic acidosis.

Under normal conditions, propylene glycol is rapidly converted to lactic acid, which is cleared by the liver. We estimate that our patient received approximately 500 g of propylene glycol during the 10-hour infusion. As propylene glycol has a clearance of approximately 0.1 L/kg/hour, the peak serum concentration at steady state for a 70-kg man receiving 50 g/hour would be approximately 700 mg/dl, which is very similar to the observed concentration of 659 mg/dl.

In one case series, the total propylene glycol dose resulting in toxicity ranged from 444–970 g over 5–7 days,¹ whereas another reported an average dose of 1.2 g/day.² In general, the acidosis in these cases was less severe than in our patient and resolved without treatment. Our patient responded to fomepizole and hemodialysis, the standard treatments for toxic alcohol poisoning. Other reports also describe the use of fomepizole for propylene glycol poisoning after prolonged infusion.^{3, 4} Fomepizole acts by inhibiting alcohol dehydrogenase, the first step in metabolism of propylene glycol. Thus, the metabolite, lactic acid, is not formed. Fomepizole is approved by the United States Food and Drug Administration for the treatment of methanol and ethylene glycol toxicity, and prevents the formation of the toxic metabolites of formate, in the case of methanol poisoning, and glycolic and oxalic acids, in the case of ethylene glycol poisoning. Our patient's prompt response to these therapies suggests that this treatment is also useful for acute propylene glycol overdose. If our patient's overdose had been recognized sooner, it is likely that early administration of fomepizole would have prevented the need for dialysis.

Ethanol may also interfere with the formation of metabolites from other alcohols. Alcohol dehydrogenase preferentially metabolizes ethanol before metabolizing other alcohols. Although subsequent ethanol levels were not measured in our patient, who was a chronic ethanol abuser, he could have conceivably eliminated enough ethanol to lower his blood ethanol level to below 100 mg/dl before receiving the lorazepam infusion, thus allowing for metabolism of propylene glycol to lactate.

Several issues may limit the generalizability of our findings. Our patient was an alcoholic who likely had highly induced alcohol dehydrogenase. Furthermore, he was acutely intoxicated at the time the lorazepam infusion was started, and this would have slowed the metabolism of propylene glycol for some period. Finally, our patient had experienced a cardiac arrest and thus may have had altered hemodynamics and microcirculation, which could have altered the pharmacokinetics of propylene glycol.

Conclusion

Our patient experienced severe lactic acidosis resulting from an inadvertent 60-fold dosing error of a lorazepam infusion, which contains the

diluent propylene glycol. His lactic acidosis resolved after treatment with fomepizole and continuous venovenous hemofiltration. Clinicians should consider administering these treatments for patients with acute propylene glycol poisoning.

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