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Severe Lactic Acidosis from Iatrogenic Propylene Glycol Overdose

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Keywords

propylene glycol; iatrogenic overdose; severe lactic acidosis; critical care

Background

Propylene glycol is a diluent found in many IV and oral medications, 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 can then convert the lactate to pyruvate and metabolize the pyruvate through the Krebs cycle. Several reports have described lactic acidosis occurring during extended infusion of medications with propylene glycol diluent in an ICU setting (1,2). These cases were due to prolonged infusion of therapeutic doses, often in patients with renal dysfunction. The objective of this report is to describe a case of lactic acidosis from iatrogenic overdose of lorazepam with a propylene glycol diluent.

Case report

A 50 year-old man with a history of alcohol and cocaine abuse presented to the emergency department after a cardiac arrest caused by choking on a large piece of meat. Post cardiac arrest hypothermia protocol was initiated on arrival to the intensive care unit with 2 hours of the patient's arrival to the hospital. Cooling was continued for 24 hours. On admission his serum ethanol concentration was 406 mg/dL. Approximately 12 hours after admission he developed generalized tonic-clonic seizures that resolved after several boluses of lorazepam. Seizures were presumed to be due to anoxic brain injury from prolonged hypoxia. He was accidentally started on lorazepam at 2 mg/min instead of the standard dose of 2 mg/hr. Over the next few hours the patient became acidemic (pH 6.9) and hypotensive. Ten hours after the infusion was started, the error was recognized and the infusion was stopped. The patient's total dose of lorazepam was approximately 1.2g. The patient's mean arterial pressure on a norepinephrine infusion was between 60 and 65 mm Hg. Three hours after stopping the lorazepam infusion his arterial pH was 6.9 and serum bicarbonate was 5 meq/L, and he was started on a sodium bicarbonate infusion. His peak serum propylene glycol concentration level was 659 mg/dL, by high performance liquid chromatography method, 3 hours after infusion was stopped. At this time his serum creatinine was 0.8 mg/dL and his serum lactate was 14.6 mmol/L. The patient's serum ethanol concentration was not measured at this time, however it was 406 mg/dL on hospital admission (22 hours prior to stopping the infusion). The course of his serum propylene glycol and his serum lactate are shown in Figure 2. Four hours after stopping the infusion,

fomepizole (15 mg/kg iv followed by 10 mg/kg every 12 hours and increased to 10 mg/kg every six hours for four doses, then 15 mg/kg every six hours during renal replacement therapy) was administered. Continuous renal replacement therapy was initiated 18 hours after lorazepam infusion had been stopped. This was replaced by continuous veno-venohemofiltration once the patient's hypotension resolved (36 hours after the infusion was stopped), and continued until the patient's death. The patient's serum creatinine began to rise 42 hours into his hospitalization. He was diagnosed with acute tubulonecrosis and renal failure. At 70 hours the patient's acidosis had resolved, the serum propylene glycol concentration was 45 mg/dL, and fomepizole was discontinued. Unfortunately, he did not recover from renal failure and he suffered a hypoxic brain injury from his initial cardiac arrest. With the family's consent, the patient was extubated on hospital day 12 and expired minutes later.

Discussion

Propylene glycol toxicity is well described after prolonged dosing of infusions, especially in subjects with renal failure (3). Our subject developed a severe lactic acidosis from propylene glycol toxicity after a 10-hour infusion of 1.2 g. His serum propylene glycol concentration was among the highest ever reported, and his lactic acidosis was temporally related to his propylene glycol overdose. Other possible causes of lactic acidosis seem less likely. For example, although the patient had seizures, he did not continue to seize after the 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 ethanol alcoholic, he received dextrose IV during his stay that should have prevented ketoacidosis. Renal failure can result in high serum concentrations of uncleared acids. However, this patient had no evidence of renal failure initially with a serum creatinine of 0.8 mg/dL. Cocaine toxicity may produce an elevated lactate but the patient did not have evidence of cocaine toxicity on presentation to the ED. Nor is the time course consistent with cocaine toxicity producing an acidosis as symptoms usually develop almost immediately after ingestion or inhalation. The elevated propylene glycol level is much more likely to be the cause of this patient's 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 gm of propylene glycol during the 10-hour infusion. As propylene glycol has a clearance of approximately 0.1L/kg/hr, the peak serum concentration at steady state for a 70 kg male receiving 50 g/hr would be approximately 700 mg/dl, which is very similar to the observed concentration of 659 mg/dl.

In one series the total PG dose resulting in toxicity was between 444 g to 970 g over 5 to 7 days (1), while another reported an average daily dose of 1.2 g/day (2). In general, the acidosis in these cases has been less severe and resolved without specific therapy. Our patient responded to fomepizole and hemodialysis, the standard treatments for toxic alcohol poisoning. Previous reports described the use of fomepizole for propylene glycol poisoning following 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 currently approved 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 accidental 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 "block" the formation of other alcohols to their metabolites. Alcohol dehydrogenase preferentially metabolizes ethanol prior to metabolizing other alcohols.

Although subsequent ethanol levels are not measured, the patient who was a chronic ethanol abuser, could have conceivably eliminated enough ethanol to lower his blood ethanol level to below 100 mg/dL prior to receiving the lorazepam infusion, thus allowing for metabolism of propylene glycol to lactate.

There are several issues that may limit the generalizability of the findings of this report. 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 PG for some period. Finally, our patient was post-cardiac arrest. Post-cardiac arrest patients may have altered hemodynamics and microcirculation, which could have altered the pharmacokinetics of propylene glycol.

Conclusion

We describe a case of severe lactic acidosis following an inadvertent 60 fold dosing error of a lorazepam infusion. The patient's lactic acidosis resolved after treatment with fomepizole and CVVH. We believe that these treatments should be considered for patient with acute propylene glycol poisoning.

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Figure 1. Metabolism of propylene glycol to lactic acid (ADH- alcohol dehydrogenase, ALDH-aldehyde dehydrogenase).

Figure 2.

Serum propylene glycol and lactate concentrations following a 10 hour infusion of 120 mg/hr of lorazepam. The boxes show the duration of lorazepam infusion, continuous renal replacement therapy (CRRT), continuous veno-venous hemofiltration (CVVH) and the timing of the first dose of fomepizole.