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BRIEF REPORT

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Removal of propylene glycol and correction of increased osmolar gap by hemodialysis in a patient on high dose lorazepam infusion therapy

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Abstract We report a case of successful treatment of propylene glycol toxicity by discontinuation of propylene glycol administration and hemodialysis therapy. A critically ill woman receiving high dose intravenous lorazepam therapy is described. Although propylene glycol toxicity often resolves promptly after discontinuation of the causative parenteral source, renal or liver dysfunction may prolong the sequelae of propylene glycol infusion. Hemodialysis efficiently lowers propylene glycol serum concentrations in a manner analogous to extracorporeal therapy for other small molecular weight alcohol intoxications. Therefore, hemodialysis may be a useful component of therapy for critically ill patients exhibiting propylene glycol toxicity in the context of multiple organ dysfunction.

Keywords Propylene glycol · Osmolar gap · Lactic acidosis

Introduction

Propylene glycol is an excipient often used in pharmaceuticals to enhance solubility. Although it is generally regarded as a benign diluent in many parenteral products (Table 1), potential safety concerns have been described since 1967 [1]. Since that time, propylene glycol toxicity has been reported in patients receiving a number of parenteral medications including etomidate, nitroglycerin and, more recently, lorazepam.

Lorazepam has been identified as one of the benzodiazepines administered to adult critically ill patients when long-term sedation is required [2]. This agent is commonly administered intravenously in high doses for prolonged periods and occasionally in high doses in patients with multiple organ system dysfunction. Five case reports and an abstract with eight patients comprise the available literature regarding propylene glycol toxicity with lorazepam infusion [3, 4, 5, 6, 7, 8]. Prominent toxicities described include renal dysfunction, lactic acidosis and hyperosmolar states. We present a patient with an extreme osmolar gap that was associated with propylene glycol, and demonstrate that hemodialysis effectively clears propylene glycol and can enhance the resolution of hyperosmolality.

Case report

A 34-year-old Caucasian female presented to the Emergency Department with a 4day-old vesicular rash, which became diffuse and was associated with increasing dyspnea on the day of presentation. Her past medical history included an anxiety disorder marked by frequent panic attacks for which she received buspirone and frequent benzodiazepines as an outpatient. She consumed five glasses of wine and smoked 20 cigarettes daily. Her chest radiograph revealed diffuse airspace abnormalities and her laboratory studies were significant for a normal acid-base status and nor-

mal renal function. She was started on intravenous acyclovir but, on hospital day 2, had worsening dyspnea and hypoxemia despite a high-flow oxygen mask. She was transferred to the ICU, remained hypoxemic after intubation (PO_2/FIO_2=58 on 5 cmH_20 PEEP) and was diagnosed with the adult respiratory distress syndrome (ARDS) complicating varicella pneumonia.

Over the next 24 h her ventilatory support escalated to pressure control ventilation with a tidal volume of 7 ml/kg, and 14 cmH_20 PEEP with persistent hypoxemia (PO_2/FIO_2=47). To allow prone ventilation, she required a continuous infusion of fentanyl (50 µg/h) and lorazepam (6 mg/h). Her ICU course over the next 3 days was complicated by disseminated intravascular coagulopathy with associated necrosis of the tips of her fingers and toes, metabolic acidosis and oliguric renal failure. She was treated with antithrombin III and heparin infusions, and continuous venovenous hemofiltration. By ICU day 8, she required an FIO_2 of 0.5, 14 cmH_20 PEEP and higher doses of fentanyl (150 µg/h) and lorazepam (10 mg/h) to tolerate ventilation and other care. She developed bilateral pneumothoraces requiring chest tube placement. Because of ongoing high minute ventilation requirements (19 l/min), she underwent tracheostomy on ICU day 10. Attempts to reduce her sedative regimen resulted in agitation, tachypnea and obvious distress and she was maintained on lorazepam (up to 24 mg/h) and fentanyl (up to 150 µg/h) infusions pending further improvement in ventilation and oxygenation. Her renal replacement therapy was converted to intermittent hemodialysis.

On ICU day 24, a previously mild anion gap worsened to 18 (sodium 131 mEq/l, chloride 95 mEq/l, bicarbonate 18 mEq/l, arterial pH 7.28, $PaCO_2$ 42 mmHg, calculated bicarbonate 20 mEq/l, PaO_2 86). A pulmonary artery catheter was inserted which revealed a cardiac output of 7.6 l/min and systemic vascular resistance of 832 dyne·s·cm^{-5}. She had a fever, an increased white blood cell count of 25,600 cells/dl with 68% polymorphonuclear cells and 13% bands on the differential count and a urine culture which grew *Enterococcus*. Blood cultures and sputum culture remained sterile. Serum lactate was 2.7 mmol/l. Despite aggressive care with broad spectrum antibiotics and more frequent hemodialysis, the acidosis did not resolve. As part of a continued evaluation, an osmolar gap was identified and suspected to be associated with propylene glycol from the high dose lorazepam infusion. At this point, the 24day cumulative lorazepam and propylene glycol doses were 7226 mg and 2890 ml, respectively.

On the subsequent day, dialysis was again performed. A femoral vein temporary dialysis catheter was used. The treatment duration was 6 h, using an Althin Altra Nova 200 hemodialyzer. This dialyzer has a cellulose acetate-N membrane with the following characteristics: surface area of 2.2m^2, KOA (at Q_B=300) of 641 and KUF of 9.2 ml/mmHg per h. Mean blood flow was 300 ml/min and dialysate flow was 500 ml/min. Net ultrafiltration was 7 kg. Electrolytes, blood urea nitrogen, glucose, serum osmolality and propylene glycol levels were measured at the start of dialysis therapy, 2 h after therapy completion and again the next morning (Table 2). Following dialysis, a significant reduction was seen in the osmolar gap and propylene glycol serum concentration. The metabolic acidosis resolved.

She was converted to enteral lorazepam administration and propofol for sedation, enteral administration of clonidine was added and she was eventually converted to phenobarbital, which prevented benzodiazepine withdrawal symptoms and facilitated tapering of her sedation medications. She eventually was liberated from ventilatory support on ICU day 78, left the ICU on day 88 and was discharged home on hospital day 105.

Table 1 Parenteral pharmaceutical preparations containing propylene glycol

Medication	Percentage propylene glycol
Chlordiazepoxide (Librium)	20
Diazepam (Valium)	40
Digoxin (Lanoxin)	40
Esmolol (Brevibloc)	25
Etomidate (Amidate)	35
Hydralazine (Apresoline)	40
Lorazepam (Ativan)	80
Multivitamin injection (MVI-12)	30
Nitroglycerin (Tridil)	30
Phenobarbital	70
Phenytoin (Dilantin)	40
Trimethoprim/Sulfamethoxazole (Bactrim)	40

Discussion

Propylene glycol toxicity is increasingly recognized as a complication of high dose intravenous lorazepam therapy. Large volumes of the diluent are used as the drug vehicle. Similar toxicity is sometimes observed when this diluent is the vehicle for high dose infusions of other intravenous medications. The pathways of biometabolism of this compound and features of toxicity, including acute renal failure, increased osmolar gap and lactic acidosis, have recently been reviewed [4].

Propylene glycol toxicity has been primarily attributed to the parent compound and its end pathway metabolite, lactate [3, 4, 5, 6, 7, 8, 9]. The relationship between

Table 2

	Pre-dialysis	2 h post-dialysis	12 h post-dialysis
Measured serum osmolality	380	319	312
Calculated serum osmolality[a]	283	292	291
Osmolar gap[b]	97	27	21
Propylene glycol (mg/dl)	520	170	N/A
Osmolar gap corrected[c]	28	5	N/A
Anion gap	18	15	13

[a] $Calculated\ serum\ osmolality = (2 \times [NA^+]) + \frac{Glucose}{18} + \frac{blood\ urea\ nitrogen}{2.8}$

[b] Osmolar gap = measured serum osmolality–calculated serum osmolality

[c] $Estimated\ osmolar\ effect\ of\ propylene\ glycol = \frac{Propylene\ glycol}{7.6}$ [4]

toxicity and serum concentrations is not well described. Those prone to propylene glycol accumulation and its potential adverse events include patients with impaired alcohol and aldehyde dehydrogenase enzyme systems such as children under the age of 4, pregnant women, those with severe renal or hepatic disease and those treated with disulfiram or metronidazole. Propylene glycol is oxidized by hepatic alcohol dehydrogenase to intermediate metabolites, lactaldehyde and methylglyoxal, and then to lactate and pyruvate. In the context of normal renal and liver function and mild or moderate blood levels, the duration of toxicity is brief and easily reversible due to the brief terminal half-life of propylene glycol, ranging from 1.4 to 3.3 h in adults [10]. Formal study of the pharmacokinetics of this agent in impaired renal or liver states has not been performed. It is reasonable to assume that the half-life would be prolonged in established renal failure since 15–45% of the parent compound is excreted by the kidneys. In addition, renal and/or hepatic impairment would limit intrinsic mechanisms for correcting lactic acidosis. In such circumstances, extracorporeal removal of the parent compound may be desirable in order to abrogate its toxic potential.

Propylene glycol is an alcohol of small molecular weight, 76.1 daltons. Other small molecular weight alcohols are known to be toxic or lethal when present in high serum concentrations. Ethylene glycol and methanol are metabolized to toxic products. Isopropyl alcohol is directly toxic and also has toxic metabolites. These agents share several properties which favor excellent clearance by hemodialysis, including small size, non-ionic state, high water solubility and lack of significant serum protein binding [11]. Hemodialysis is an efficient and timely therapy for such intoxication. Propylene glycol would be expected to have similar properties.

At least one group has observed correction of hyperosmolality and osmolar gap with hemodialysis therapy in a patient with a propylene glycol level of 16 mg/dl [12]. However, the patient was also receiving mannitol, and pre-dialysis lactate and post-dialysis propylene glycol were not measured. In the present case, we postulated that propylene glycol would be efficiently removed by hemodialysis therapy. There was a threefold reduction in propylene glycol levels post-dialysis. In the context of normal renal and liver function, it is conceivable that the reduction in propylene glycol could be attributed to endogenous clearance and metabolism alone. However, it is probable that the half- life for propylene glycol was significantly prolonged in her state of critical illness, including acute renal failure. Moreover, the osmolar gap did not change significantly in the 14h interval after dialysis. Rebound phenomena cannot account for the latter finding since we waited 2 h to obtain the first post-dialysis level and the small molecular weight alcohols are not highly lipid bound.

The osmolar gap, as a surrogate marker for circulating propylene glycol, dropped proportionately to propylene glycol serum concentrations. The osmolar gap may have great clinical utility for this intoxication as few hospital laboratories are equipped to monitor serum propylene glycol concentrations. Critical analysis of our data shows that propylene glycol predominated, but did not fully account for the osmolar gap at the highest (pre-dialysis) serum concentrations. Propylene glycol did sufficiently represent the osmolar gap in the post-dialysis measures. Review of her other medications and nutrient infusions did not reveal another source for unmeasured osmoles pre-dialysis. It is possible that the intermediate metabolites, lactaldehyde and methylglyoxal, or polyethylene glycol-400, another diluent in lorazepam injection, contributed a small component to the osmolar gap. We did not assay for these compounds.

In summary, we observed evidence of propylene glycol intoxication in a patient who had received high dose lorazepam therapy for a prolonged duration. Hemodialysis significantly reduced the serum concentrations of propylene glycol. Extracorporeal removal of propylene glycol may be particularly useful in states of renal or hepatic dysfunction. Further study of the pharmacokinetics of propylene glycol in critical illness as well as the kine-tics of its extracorporeal extraction and clearance are needed in order to understand better the toxicology of, and potential therapies for, this common drug vehicle.

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