

Acute kidney injury, hyperosmolality and metabolic acidosis associated with lorazepam

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SUMMARY

Background A 54-year-old male with a history of multiple admissions for alcohol intoxication was admitted to hospital with right flank pain. He received a high-dose lorazepam infusion for alcohol withdrawal during hospitalization and developed severe hyperosmolality, high anion gap metabolic acidosis, and acute kidney injury on his eighth day of hospitalization.

Investigations Serum chemistries, arterial blood gas analysis, and measurement of serum propylene glycol, ethylene glycol and methanol levels.

Diagnosis Propylene glycol toxicity.

Management Discontinuation of lorazepam infusion, administration of fomepizole, hemodialysis for five consecutive days, hemodynamic support, and follow-up of serum osmolality as a measure of propylene glycol decay.

KEYWORDS acute kidney injury, hyperosmolality, lorazepam adverse effects, metabolic acidosis, propylene glycol toxicity

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THE CASE

A 54-year-old white male with a past medical history of multiple admissions for alcohol intoxication was admitted with right flank pain. A CT scan revealed a small right psoas hematoma. The patient was managed conservatively, and he developed severe alcohol withdrawal 2 days later. He was started on an intravenous infusion of lorazepam, intravenous fluids, thiamine and multivitamins, as per hospital protocol. On the fifth day of hospitalization, the patient required higher doses of lorazepam (>5 mg/hour) and was transferred to the intensive care unit as a precautionary measure. On the eighth day of hospitalization, the patient developed severe metabolic acidosis (pH 7.11) and acute kidney injury (AKI; see Table 1).

The patient was suspected of having propylene glycol toxicity secondary to prolonged infusion of high-dose lorazepam (approximately 10–20 mg/hour averaged over 8 days). Lorazepam infusion was stopped immediately and a new set of laboratory values were obtained, including serum propylene glycol, methanol and ethylene glycol levels and serum osmolality. The patient's condition deteriorated dramatically over the next few hours and he required intubation and hemodynamic support. The new data revealed an impressive osmolal gap of 145 mmol/kg (normal 10 mmol/kg). Hyperosmolality, metabolic acidosis and AKI are classic signs of propylene glycol toxicity in patients receiving high-dose lorazepam. As propylene glycol is metabolized by alcohol dehydrogenase, one dose of fomepizole (a competitive inhibitor of alcohol dehydrogenase; 15 mg/kg intravenously) was given. The treatment of choice in such cases, however, is hemodialysis. The patient described here underwent emergency hemodialysis for 4 hours on the eighth day of hospitalization.

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Table 1 Hospital course and management.

Laboratory parameter	Value on hospital day 7	Value on hospital day 8 ^a	Value on hospital day 9	Value on hospital day 10	Value on hospital day 11
Serum sodium, mmol/l	133	119	129	135	136
Serum potassium, mmol/l	3.8	4.9	3.7	3.5	3.5
Serum chloride, mmol/l	100	92	95	99	101
Serum carbon dioxide, mmol/l	23	13	24	31	30
Blood urea nitrogen, mmol/l (mg/dl)	2.1 (6)	5.0 (14)	3.6 (10)	3.2 (9)	4.6 (13)
Serum creatinine, μ mol/l (mg/dl)	79.6 (0.9)	168.0 (1.9)	123.8 (1.4)	70.7 (0.8)	79.6 (0.9)
Serum glucose, mmol/l (mg/dl)	7.7 (138)	6.8 (123)	10.2 (183)	8.4 (152)	5.9 (106)
Anion gap, mmol/l	10	14	10	5	5
L-lactic acid, mmol/l	ND	6.1	2.8	1.1	0.8
Measured serum osmolality, mmol/kg	ND	395	344	321	321
Calculated serum osmolality, mmol/kg	ND	249	271	281	282
Osmolal gap, mmol/kg	ND	145	72	39	38

^aPatient started on hemodialysis. Abbreviation: ND, not done.

The diagnosis of propylene glycol toxicity was confirmed by a high serum propylene glycol level (810 mg/dl) in a blood sample that had been obtained before the first dialysis session. Serum ethylene glycol and methanol levels were undetectable in this sample. Daily hemodialysis (4 hours/day) was continued for the next 5 days. As osmolal gap correlates closely with serum propylene glycol level, the patient's daily osmolal gap was monitored in order to estimate propylene glycol decay. After the second dialysis session, his osmolal gap had improved to 39 mmol/kg. Gradual clinical and metabolic improvements were seen over the next week.

DISCUSSION OF DIAGNOSIS

Propylene glycol (1,2-propanediol) is commonly used as a solvent in intravenous, oral and topical pharmaceutical preparations (Table 2).¹⁻⁵ The agent is generally considered safe, but large doses can be toxic, particularly if they are given over a short period of time. Of the commonly used intravenous drugs containing propylene glycol, intravenous lorazepam contains the largest proportion of the compound. Each milliliter of Ativan[®] (Wyeth-Ayerst Laboratories, American Home Products Corporation, Delaware, NY) injection (dosage strength 2 mg of lorazepam per ml) contains 0.8 ml (830 mg) of propylene glycol and 0.18 ml of polyethylene glycol.³ The patient presented here received a cumulative lorazepam dose of 4,094 mg over an infusion

period of 7 days, which is the equivalent of 1,638 ml (1,699 g) of propylene glycol (molecular weight 76 Da) and 368 ml of polyethylene glycol (molecular weight 400 Da). In any parenteral lorazepam dose, propylene glycol contributes nearly 23 times as many osmotically active particles as does polyethylene glycol.³

Pathophysiology and metabolism of propylene glycol

The mechanism of propylene glycol toxicity is unclear.^{1,2} No convincing *in vivo* evidence exists to blame either byproducts or direct cytotoxicity by propylene glycol.^{1,2} Accumulation of propylene glycol leads to increased osmolality and lactic acidosis, which in turn causes hyperosmolality and high anion gap metabolic acidosis. Studies have shown accumulation of propylene glycol in patients who have received a high-dose lorazepam infusion for as little as 48 hours.² AKI in propylene glycol toxicity has been suggested to be caused by proximal tubular injury.⁶

The patient presented here developed both high and normal anion gap metabolic acidosis (Table 1). While the high anion gap metabolic acidosis was probably secondary to lactic acidosis, the normal anion gap metabolic acidosis might be attributable to the prolonged intravenous fluid infusion or to an inability of the kidneys to regenerate bicarbonate because of the proximal tubular injury.

Table 2 Commonly used intravenous drugs that contain propylene glycol.

Drug and concentration	Amount of propylene glycol (% v/v)
Lorazepam, 2 mg/ml	80
Phenobarbital, 30–130 mg/ml	67.8–75.0
Diazepam, 5 mg/ml	40
Pentobarbital, 50 mg/ml	20–40
Phenytoin, 50 mg/ml	40
Trimethoprim–sulfamethoxazole, 16 mg/ml:80 mg/ml	40
Etomidate, 2 mg/ml	35
Nitroglycerin, 5 mg/ml	30
Esmolol, 250 mg/ml	25

Adapted with permission from Lippincott Williams & Wilkins © Arroliga AC *et al.* (2004) Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. *Crit Care Med* **32**: 1709–1714.²
Abbreviation: v/v, volume/volume.

Severe thiamine deficiency can also lead to lactic acidosis.⁷ Although the patient's thiamine level was not checked, he was receiving thiamine supplements during hospitalization.

Reynolds and colleagues attributed the major toxic effects of propylene glycol to proximal renal tubular injury rather than to lactic acidosis or hyperosmolality. In their case study they showed, by regression analysis, that bicarbonate levels were significantly influenced by the presence or absence of lorazepam infusion (i.e. serum bicarbonate level did not rise in response to hypercarbia when the patient was receiving lorazepam). These findings indicate that propylene glycol interferes with proximal tubular bicarbonate regeneration.⁸ Elegant studies by Morshed *et al.* that assessed the acute toxicity of propylene glycol using cultured proximal tubular cells of human origin indicated the rapid onset of cellular toxicity (i.e. within 10 minutes) even when plasma membrane integrity and viability seemed normal.⁹ An overt morphological presentation of proximal tubular damage is cellular edema, cytoplasmic vacuolization, hydropic degeneration and necrosis.^{8,10–12} The glomerulus and distal tubules are usually spared.¹³ Although these observations show proximal tubular injury to be at the center of propylene glycol toxicity, propylene-glycol-induced lactic acidosis associated with clinical deterioration has also been observed in patients with no laboratory evidence of AKI.¹⁴

In adults with normal hepatic and renal function, the terminal half-life of propylene glycol is within the range 1.4–3.3 hours.¹³ Commercial

propylene glycol is a 50:50 mixture of D and L isomers of propylene glycol. Approximately 45% of an absorbed propylene glycol dose is excreted unchanged by the kidneys. The remaining 55% is metabolized by hepatic alcohol dehydrogenase to D and L isomers of lactaldehyde or methylglyoxal. In the presence of aldehyde dehydrogenase, D-lactaldehyde and L-lactaldehyde are converted to D-lactate and L-lactate. Methylglyoxal is metabolized to D-lactate. L-lactate enters the gluconeogenic pathway and serves as an important source of glucose and glycogen. D-lactate is thought to be metabolized to pyruvate and carbon dioxide by D-2-hydroxyacid dehydrogenase, but does not significantly contribute to gluconeogenesis.¹⁴ Although lactic acidosis in propylene glycol toxicity is often attributed to L-lactate accumulation, severe D-lactic acidosis has also been reported in some cases.¹⁵ Unfortunately, D-lactate levels were not measured in the patient presented here. With the above knowledge, it would be useful to check both D- and L-lactic acid levels in patients with suspected propylene glycol toxicity. As a result of the stereospecific preference of mammalian alcohol dehydrogenase and aldehyde dehydrogenase for L-propylene glycol, this stereoisomer is cleared most rapidly, and it has been suggested that neurologic dysfunction occurring in propylene glycol toxicity is caused by the accumulation of D-propylene glycol and D-lactate.¹³

A normal or acceptable level of propylene glycol has not yet been defined. As a result, the clinical implications of surveillance of propylene

Box 1 Clinical and laboratory findings associated with acute propylene glycol toxicity reported in humans.

Acute kidney injury
 Hyperosmolality
 Lactic acidosis
 Central nervous system depression (confusion, lethargy, drowsiness, stupor, coma, apnea)
 Seizures
 Hypotension
 Hypotonia
 Hyponatremia
 Hypoglycemia
 Hemolysis
 Hemoglobinuria
 Intracranial hemorrhage
 Bradycardia and QRS and T abnormalities on the electrocardiogram
 Arrhythmia
 Cardiac arrest
 Sepsis
 Systemic inflammatory response (SIRS)-like syndrome

Box 2 Predisposing factors for propylene glycol toxicity.

Rapid and prolonged use of medications containing propylene glycol
 Use of a combination of medications containing propylene glycol
 Renal insufficiency
 Hepatic insufficiency
 Alcohol abuse
 Pregnancy
 Age <4 years
 Use of disulfiram and metronidazole
 Critical illness

glycol levels are unclear. Chicella and colleagues evaluated the impact of lorazepam infusion in 11 children (aged 1–15 months). Although significant increases in propylene glycol levels were observed during the study, no adverse effects, increases in anion gap or hyperosmolality were noted.¹⁶ One report showed that patients with clinical deterioration related to propylene glycol toxicity had serum propylene glycol levels that ranged from 104 mg/dl to 144 mg/dl; by contrast, patients with only metabolic abnormalities had serum propylene glycol levels in the range 58–127 mg/dl.¹

The World Health Organization recommends a maximum dietary propylene glycol intake of 25 mg/kg/day (i.e. 1,875 mg/day for a 75 kg male).¹⁷ The patient described here received an average intravenous propylene glycol dose of 212 g/day (2,827 mg/kg/day).

Clinical presentation of propylene glycol toxicity

Classically, propylene glycol toxicity results in lactic acidosis, hyperosmolality and renal failure.^{1–4,17,18} Clinical presentation of this condition varies widely, however, sometimes even mimicking sepsis or systemic inflammatory response syndrome (Box 1).¹ If unrecognized and left untreated, the toxic effects of propylene glycol can progress from metabolic acidosis to fatal multiorgan failure. In a case series of patients receiving lorazepam infusions, none of the

patients exhibited significant clinical deterioration despite the fact that metabolic evidence of propylene glycol toxicity was present in 19% of them. This finding indicates that the spectrum of propylene glycol toxicity ranges from metabolic abnormalities (which are common) to clinical deterioration (which occurs infrequently).¹

AKI can reverse following discontinuation of lorazepam infusion, as shown by Yaucher and colleagues in their report of 128 patients who received high-dose lorazepam. Serum creatinine levels rose in eight patients, and returned to baseline in seven of these when lorazepam was discontinued.⁶

Risk factors and incidence of propylene glycol toxicity

Risk factors for propylene glycol toxicity that are commonly recognized in the literature are listed in Box 2. The patient presented here was an alcoholic and had compromised liver function that could have been easily overwhelmed by the high propylene glycol load.

Some authors have suggested that individuals with a history of ethanol abuse might be particularly susceptible to propylene glycol toxicity as both ethanol and propylene glycol are metabolized by similar mechanisms. Long-standing ethanol abuse has been hypothesized to alter the normal metabolic pathways, resulting in hyperosmolality and lactic acid production.¹ Ethanol-related inhibition of propylene glycol metabolism has also been proposed to explain the presence of high propylene glycol levels in a patient who had simultaneously ingested ethanol and automotive antifreeze containing propylene glycol.¹⁹

Simultaneous administration of more than one medication containing propylene glycol can also

result in propylene glycol toxicity. Hayman and colleagues reported a case of acute tubular necrosis with propylene glycol toxicity in a patient who had received concomitant intravenous lorazepam and trimethoprim–sulfamethoxazole.¹⁰

Recognizing propylene glycol toxicity

Propylene glycol toxicity should be considered in any patient who is receiving medications that use propylene glycol as a solvent and who develops high anion gap metabolic acidosis, hyperosmolality or acute kidney injury.

Osmolal gap at 48 hours is considered to be the strongest marker of propylene glycol concentration; by contrast, anion gap and serum lactate concentrations are poor indicators.^{1,2,18} Arroliga *et al.* showed significant correlation between the rate of high-dose lorazepam infusion, serum propylene glycol level and serum osmolality at 48 hours (Figures 1 and 2). Serum propylene glycol concentration can be predicted using the following equation: serum propylene glycol concentration (mg/dl) = $-82.1 + (\text{osmolal gap [mmol/kg]} \times 6.5)$.² The osmolal gap can be corrected for the osmolar contribution of propylene glycol by dividing the propylene glycol level by 7.6.

DISCUSSION OF TREATMENT

Propylene glycol is a low molecular weight (76.1 Da), nonionic, highly water-soluble alcohol. This agent does not exhibit significant serum protein binding and is thus dialyzable.²⁰ Intermittent hemodialysis is the preferred therapy for propylene glycol toxicity.²⁰ Surprisingly, propylene glycol toxicity has also been reported in a patient who was already receiving continuous venovenous hemofiltration with dialysis.²¹ A closer look at this case indicated that propylene glycol toxicity had developed as a result of the combination of impairment of liver function and continued high-dose propylene glycol exposure. Toxicity resolved with discontinuation of lorazepam and ongoing continuous venovenous hemofiltration with dialysis.²¹ Parker *et al.* demonstrated the efficacy of intermittent hemodialysis in resolving propylene glycol toxicity.²⁰ In their report, hemodialysis resulted in excellent propylene glycol clearance, which correlated with an improvement in serum osmolality with no evidence of a rebound phenomenon.²⁰ The patient presented here received one dose of fomepizole. The impact of this intervention was not determined, however, since the patient

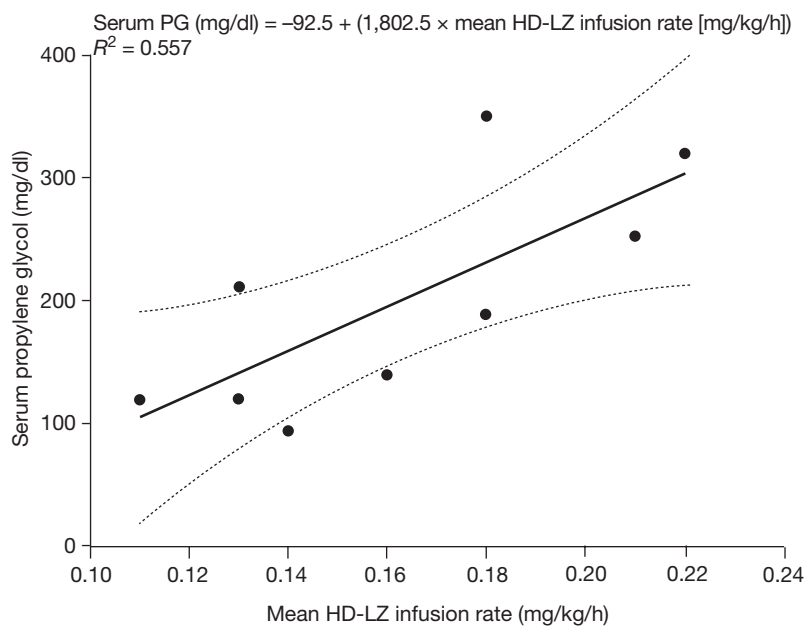


Figure 1 Correlation between rate of infusion of high-dose lorazepam and serum propylene glycol concentrations at 48 hours. Adapted with permission from Lippincott Williams & Wilkins © Arroliga AC *et al.* (2004) Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. *Crit Care Med* **32**: 1709–1714.² Abbreviations: HD, high-dose; LZ, lorazepam; PG, propylene glycol; R^2 , coefficient of determination.

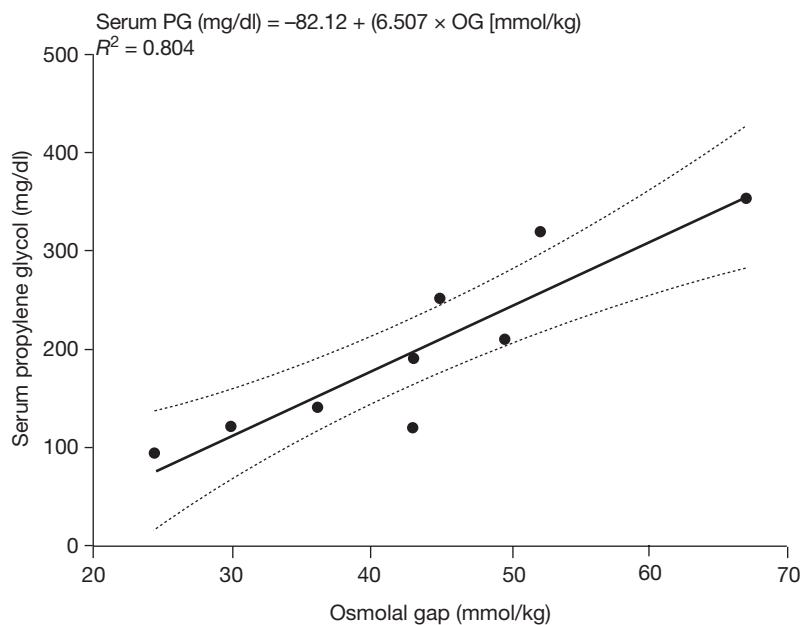


Figure 2 Correlation between serum propylene glycol concentration and osmolal gap at 48 hours. Adapted with permission from Lippincott Williams & Wilkins © Arroliga AC *et al.* (2004) Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. *Crit Care Med* **32**: 1709–1714.² Abbreviations: OG, osmolal gap; PG, propylene glycol; R^2 , coefficient of determination.

Competing interests

The authors declared no competing interests.

was started on hemodialysis soon afterwards. No clear evidence can be found in the current literature to support the use of fomepizole for propylene glycol or polyethylene glycol toxicity.³

Current guidelines state that intravenous lorazepam should be given at 0.01–0.1 mg/kg/h.¹ Patients receiving a continuous infusion of high-dose lorazepam (>10 mg/h) for greater than 48 hours should be monitored for propylene glycol toxicity.² The patient presented here received approximately 0.284 mg/kg/h (21.3 mg/h) of lorazepam.

CONCLUSIONS

Propylene glycol toxicity should be strongly suspected in patients hospitalized for alcohol withdrawal who are receiving high-dose lorazepam infusion and who develop hyperosmolality, high anion gap metabolic acidosis or AKI. Serum osmolality should be monitored in any patient who receives a high-dose lorazepam infusion for more than 48 hours, even in the absence of clinical features.

Propylene glycol toxicity is a potentially life-threatening iatrogenic condition that is both avoidable and treatable. Intensive care units need to define recommendations for the prevention of lorazepam-associated propylene glycol toxicity, particularly in high-risk patients (Box 2). Alternative sedatives include midazolam, propofol and narcotics, none of which contains propylene glycol.

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