

REVIEW ARTICLE

Propylene Glycol Toxicity in Children

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Propylene glycol (PG) is a commonly used solvent for oral, intravenous, and topical pharmaceutical agents. Although PG is generally considered safe, when used in high doses or for prolonged periods, PG toxicity can occur. Reported adverse effects from PG include central nervous system (CNS) toxicity, hyperosmolarity, hemolysis, cardiac arrhythmia, seizures, agitation, and lactic acidosis. Patients at risk for toxicity include infants, those with renal or hepatic insufficiency, epilepsy, and burn patients receiving extensive dermal applications of PG containing products. Laboratory monitoring of PG levels, osmolarity, lactate, pyruvate, bicarbonate, creatinine, and anion gap can assist practitioners in making the diagnosis of PG toxicity. Numerous studies and case reports have been published on PG toxicity in adults. However, very few have been reported in pediatric patient populations. A review of the literature is presented.

INDEX TERMS: adverse effects, pediatric, propylene glycol, toxicity

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INTRODUCTION

Propylene glycol (1, 2-propanediol) is an organic compound with multiple uses including: drug solvent, humectant food additive, and as a moisturizer in medicines, cosmetics, and tobacco products. Propylene glycol (PG) has been used as a carrier in fragrance oils; non-toxic antifreeze for winterizing drinking water systems; as a coolant in liquid cooling systems; and is the main ingredient in deodorant sticks. In 1982, the US Food and Drug Administration classified PG as a compound that is “generally regarded as safe.” Although considered safe for use as a vehicle for intravenous medications, PG toxicity has been reported.¹

Adverse effects of PG have occurred following topical, oral, and intravenous administration.^{2–5} The adverse effects associated with PG include CNS toxicity, hyperosmolarity, hemolysis, cardiac arrhythmia, and lactic acidosis.^{6–8} Oral and intravenous multivitamin preparations containing PG have been associated with adverse effects. A 15-month-old boy who received large doses of vitamin C suspended in PG had episodes of unresponsiveness, tachypnea, tachycardia, dia-

phoresis, and hypoglycemia.³ Seizures have been reported following ingestion of PG used as a vehicle to administer vitamin D.⁴ Hyperosmolarity in small infants has also been reported following the intravenous administration of a multivitamin preparation containing PG.⁵

In 1974, the World Health Organization recommended a maximum dose of 25 mg/kg/day of PG when ingested as a food additive. This limit does not address its use as a drug solvent. A safe maximum intravenous PG dose has not been reported in the literature. However, one study reported that serum levels of PG greater than 18 mg/dL can be toxic.⁹ Other investigators have shown that toxicity is most likely to occur when the serum PG concentrations exceed 25 mg/dL.^{10,11}

This review article is intended to aid prescribers in recognizing PG toxicity and provide prescribing guidelines for pediatric patients.

METHODS

A systematic literature search was performed using keywords: propylene glycol, PG, PG toxicity, pediatrics, and neonates. The search was limited to studies between 1970 and 2010,

Table 1. Parenteral Pharmaceutical Preparations Containing Propylene Glycol¹⁵

Drug and Concentration	Percent PG (v/v)
Diazepam 5 mg/mL	40
Digoxin 0.25 mg/mL	40
Esmolol 250 mg/mL	25
Etomidate 2 mg/mL	35
Hydralazine 20 mg/mL	40
Lorazepam 2 mg/mL, 4 mg/mL	80
Multivitamin (MVI 12)	30
Nitroglycerin 5 mg/mL	30
Pentobarbital 50 mg/mL	40
Phenobarbital 65 mg/mL, 130 mg/mL	70
Phenytoin 50 mg/mL	40
Sulfamethoxazole/Trimethoprim, 80 mg SMX/16 mg TMP/mL (Bactrim)	40

published in English and those involving human participants. The medical literature included case reports, retrospective and prospective studies, prospective controlled observational studies, and review articles. The search was further limited to adult and pediatric abstracts and full text articles relevant to the topic. Reference lists for selected retrieved articles were also reviewed.

PHARMACOKINETICS, PATHOPHYSIOLOGY, AND CLINICAL PRESENTATION

PG is primarily eliminated via the kidneys (12%-45%), with the remainder being metabolized in the liver to form lactate, acetate, and pyruvate.^{12,13} In adults with normal liver and kidney function, the terminal half-life of PG ranges from 1.4 to 3.3 hours.¹⁴ In contrast, the mean half-life is significantly longer in infants 19.3 hours (range, 10.8-30.5 hours) due to decreased renal elimination.^{2,5} Renal elimination decreases as the dose administered increases (390 mL/min/1.73 m² at a dose of 5 g/day) versus 144 mL/min/1.73 m² at a dose of 21 g/day.^{13,14} A list of intravenous medications containing PG along with their percent PG volume/volume contents is noted in Table 1.

Studies suggest that serum PG concentrations correlate positively with the duration¹² or rate^{13,16} of lorazepam infusion. However, the level beyond which PG accumulation is detrimental is still unknown. Wilson et al¹⁷ reported clinical deterioration in patients with PG levels ranging from 104 to 144 mg/dL. In contrast, in subjects with only metabolic abnormalities, the same authors found serum PG levels ranging from 58

to 126 mg/dL. The authors suggest that higher concentrations of PG are more likely to be associated with clinical deterioration.¹⁷

Laboratory values can assist a practitioner in making the diagnosis of PG intoxication. The most common include osmolality, lactate and pyruvate concentrations, in addition to bicarbonate level, serum creatinine, and anion gap. A definitive diagnosis is determined by serum PG concentrations. However, most institutions do not have the capability of running PG levels and therefore must send them to a specialty laboratory outside of the institution, which can delay confirmation of the diagnosis.⁴

Byproducts of alcohol metabolism, i.e., elevated lactate and/or pyruvate levels, are increased in patients receiving PG. The risk of metabolic acidosis increases as levels increase. If the correct diagnosis is not made, a patient can progress to hypotension, acidemia, and multisystem organ dysfunction. PG-induced intoxication can also mimic sepsis and systemic inflammatory response syndrome.^{17,18} Measurement of serum osmolality and/or a PG level can help distinguish the 2 entities; therefore, sepsis must be ruled out first.

Determination of excess serum organic acids, including lactate and pyruvate, is possible through the calculation of the anion gap. The anion gap is the difference between unmeasured anions and cations. Although many forms of metabolic acidosis are characterized by an abnormal anion gap, the accumulation of lactate, pyruvate, or exogenous toxins such as PG often produces an anion gap greater than 12 mmol/L. In the same way, the osmolal gap is the difference between

the measured and the calculated serum osmolalities. This gap is often used as a mechanism for determining the presence of low molecular weight compounds in the serum. The osmolal gap will exceed 10 mOsm/L H₂O in 2 clinical conditions: (1) decreased serum water content, in hyperlipidemia or hyperproteinemia, where the calculated osmolality is underestimated because of a falsely low serum sodium concentration, and (2) increased serum concentration of unmeasured, osmotically active, low-molecular weight compounds (<150 daltons), such as mannitol, ethanol, PG, and other alcohols.^{2,8}

Glasgow and colleagues⁵ found a direct relationship between the osmolal gap and serum PG concentrations in infants who received intravenous medications containing PG (PG = 47.5 times osmol gap + 9.2; r = 0.96). Similarly, Fligner et al² determined that the relationship between PG concentration and osmolal gap after topical administration of silver sulfadiazine was as follows:

$$\text{PG (mg/dL)} = 84.6 + (7.8 \times \text{Osmolal Gap [mOsm/kg H}_2\text{O]})$$

This calculation was based on a case report of an 8-month-old infant.

Arroliga and colleagues¹³ published a theoretical formula for predicting serum PG concentrations from the osmol gap ($-82.1 + [\text{osmol gap} \times 6.5]$) in critically ill adults receiving high dose lorazepam. However, the authors noted that this formula needs further validation and may help identify as early as 48 hours those patients at risk for PG toxicity.

In a study by Yahwak et al¹⁹ in 2008, the authors found that an osmol gap of 10 or greater was predictive of elevated PG concentrations and values of 12 or greater were predictive of clinical changes suggestive of PG toxicity. The authors also concluded that screening for PG toxicity with the osmol gap may be helpful for patients receiving intravenous lorazepam in doses greater than 1 mg/kg/day or higher.

ADVERSE DRUG REACTIONS AND PREVENTION OF PG TOXICITY

When PG is administered intravenously, adverse effects may present in different ways. With too rapid an infusion, hypotension and cardiac

arrhythmias can occur. The combination of PG and its metabolites have been implicated in various clinical scenarios such as hyperosmolality and metabolic acidosis. These conditions can lead to hemolysis, renal failure, CNS depression with seizures, and various presentations of cardiovascular decompensation.⁸

Patients with underlying kidney disease, or impaired alcohol dehydrogenase enzyme systems (e.g. children younger than the age of 4, pregnant women, patients with hepatic disease; and patients treated with disulfiram or metronidazole), are all prone to PG accumulation.¹⁶ Based on the significant renal clearance of PG, patients with underlying chronic kidney disease or newly developed acute kidney injury would be at greater risk for toxicity.¹⁸ Providers should consider a 50% reduction in the maximum daily dose in patients with underlying risk factors (liver disease, renal failure, pregnancy, concurrent treatment with metronidazole or disulfiram, age <4 years).¹⁸ Yorgin et al²⁰ reported results from a renal biopsy suggesting that renal impairment caused by PG is attributable to proximal tubular cell injury.

Table 2 provides dose limits of commonly used intravenous drugs to avoid PG toxicity based on a cumulative maximum dose of 69 g/day.¹⁸ The maximum daily dose of drug for a pediatric patient can be extrapolated from the adult data (based on a 70-kg patient).

REVIEW OF THE MEDICAL LITERATURE

Pediatric Case Reports of CNS and Cardiotoxicity Associated With PG Toxicity

In a case report by O'Donnell et al,⁸ a 32-day-old term female developed meconium aspiration pneumonitis at birth and was discharged on day 7 of life but later developed severe respiratory distress. The patient was admitted to the neonatal intensive care unit (NICU), intubated, and started on a lorazepam drip. A pump programming error resulted in the patient receiving 24 mg of lorazepam over a 1.5- to 2-hour period. The drip was discontinued and there was no evidence of PG toxicity. The next morning, the patient was restless and a lorazepam drip was restarted at 2 mg/hr and subsequently increased to 4 mg/hr. The patient continued to receive the lorazepam drip for 8 days with the rate ranging from 2 mg/hr to 7 mg/hr. On day 8, the patient began seiz-

Table 2. Dose Limits of Commonly Used Intravenous Drugs to Avoid Propylene Glycol Intoxication Based on a Maximum Amount of PG Equal to 69 g/day¹⁸

Drug	Amount of PG (mg/mL)	Maximum Daily Dose	
		Adult	Pediatrics
Lorazepam 2 mg/mL	828	166 mg/day (7 mg/hr)	2.4 mg/kg/day (0.1 mg/kg/hr)
Phenobarbital 130 mg/mL	702	12.8 g/day (533 mg/hr)	183 mg/kg/day (7.6 mg/kg/hr)
Pentobarbital 50 mg/mL	414.4	8.3 g/day (346 mg/hr)	119 mg/kg/day (4.9 mg/kg/hr)
Diazepam 5 mg/mL	414.4	832 mg/day (34.7 mg/hr)	12 mg/kg/day (0.5 mg/kg/hr)
Phenytoin 50 mg/mL	414.4	8.3 g/day (346 mg/hr)	119 mg/kg/day (4.9 mg/kg/hr)
TMP/SMX 16:80 mg/mL	414.4	2.7:13.3 g/day	39 mg/kg/day TMP component (1.6 mg/kg/hr)
Etomidate 2 mg/mL	362.6	381 mg/day (16 mg/hr)	5.4 mg/kg/day (0.2 mg/kg/hr)

PG, propylene glycol; SMX, sulfamethoxazole; TMP, trimethoprim

* Adapted from Zar et al.¹⁸

ing and the drip was increased to 6 mg/hr, and phenytoin and phenobarbital were added. The patient developed cardiovascular decompensation; dopamine and dobutamine were started, and the serum sodium, calcium, and carnitine levels were monitored. Physicians considered the hyperosmolarity (serum = 672 mOsm/kg) secondary to the PG found in the lorazepam preparation. However, other clinical features not associated with these events were the absence of an increased anion gap, absence of lactic acidosis, and absence of cardiac arrhythmias. The physicians stopped the lorazepam infusion and obtained a serum PG level. The peak anion gap occurred 9.5 hours later. The patient had an elevated serum osmolality that correlated with a wide osmolal gap. In contrast to the anion gap, the osmolal gap peaked during the lorazepam infusion and dropped steadily following its discontinuation. These values correlated with the presence of the PG parent compound.⁸

In another case report, an 8-month-old developed cardiorespiratory arrest associated with a peak serum PG concentration of 1059 mg/dL.² The infant was treated with topical silver sulfadiazine for a burn and toxic necrolysis involving 78% of his total body surface area. The day after the cardiac arrest, the osmolal gap (discrepancy between the measured and calculated osmolalities) was 74 mOsm/kg H₂O. During the course of the day, the measured serum osmolality increased to a peak of 420 mOsm/kg H₂O with a peak osmolal gap of 130 mOsm/kg H₂O. The following day, the serum glycol screen showed a large amount of PG, later quantitated at 771

mg/dL. Silver sulfadiazine was discontinued after all other medications were ruled out as a contributing source of PG. The authors reported that during the preceding 70 hours of hospitalization, the patient had received a topical PG dose of 9 g/kg/24 hr. Four days after discontinuation of the silver sulfadiazine, the patient's serum osmolality gradually decreased to 298 mOsm/kg H₂O, the osmolal gap normalized to less than 9 mOsm/H₂O, and the lactic acidosis resolved.²

SUMMARY OF THE LITERATURE

Pediatric Studies

Shehab et al²¹ conducted a retrospective, observational study in neonatal and pediatric intensive care unit patients to document neonatal exposures to the potentially harmful pharmaceutical excipients benzyl alcohol (BA) and PG. Lorazepam, phenobarbital, and digoxin were the only medications involved in the PG exposures. The authors observed a wide range in cumulative excipient doses received by neonates. The median range for PG was 204.9 (17.3-9472.7 mg/kg/day). Patients who received continuous infusions versus intermittent dosing received higher excipient doses. The median cumulative excipient doses (PG, 4554.5 mg/kg/day) were 180 times the acceptable oral daily intakes of PG (25 mg/kg/day).

Chicella et al²² conducted a prospective study in 11 intubated patients in a tertiary care pediatric intensive care unit (PICU). The author's objective was to determine if PG accumulates in children receiving continuous lorazepam infusion and, if

accumulation occurs, to determine if it is associated with significant laboratory abnormalities. The authors concluded that PG accumulated significantly in PICU patients receiving continuous lorazepam infusion and PG concentration correlated with the cumulative lorazepam dose the patient received. However, significant lab abnormalities due to PG accumulation were not observed. MacDonald et al²³ reported an increased incidence of seizures (33% vs 14%, $p = 0.21$) in low birth weight infants who received MVI-12 (PG 3 g/day), compared to infants receiving MVI concentrate (PG 300 mg/day).

TREATMENT OF PG TOXICITY

PG is a small molecular weight alcohol, 76.1 daltons, that is nonionic, highly water soluble (DVD 0.7-0.9 L/kg), and lacks significant serum protein binding, making it readily cleared by hemodialysis. Intermittent dialysis is the preferred method of treatment as it rapidly lowers PG levels (without a rebound in its level) and corrects associated metabolic abnormalities.¹⁵ In a study by Parker et al,¹⁵ the authors report that hemodialysis significantly reduced serum concentrations of PG.

CONCLUSION

Although PG is considered safe for use as a vehicle for intravenous medications by the US Food and Drug Administration, at high levels, PG can accumulate and cause lactic acidosis, CNS depression, coma, hypoglycemia, seizures, and hemolysis. Patients at risk for toxicity include infants, patients with renal insufficiency, patients with epilepsy, or burn patients who receive extensive dermal applications of PG. PG toxicity can occur at dosing of lorazepam as low as 4 to 6 mg per hour in adults. The clinical diagnosis of PG intoxication may be difficult since many institutions do not measure PG levels. However, the osmolar gap, anion gap, and lactate are commonly elevated in PG intoxication.

Practitioners should exercise caution when treating patients with large doses or prolonged use of medications containing PG especially in infants or patients with renal or hepatic dysfunction. Propylene glycol toxicity should be suspected in any patient with an unexplained anion gap, metabolic acidosis, hyperosmolarity, and/

or clinical deterioration who has received drug therapy with PG as a drug solvent. Additional studies in the pediatric population are warranted.

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Abbreviations BA, benzyl alcohol; CNS, central nervous system; NICU, neonatal intensive care unit; PG, propylene glycol; PICU, pediatric intensive care unit.

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