Case Report

Propylene glycol-induced lactic acidosis in a child receiving a pentobarbital continuous infusion

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Abstract. Pentobarbital (PB) contains 40% propylene glycol (PG) and could result in lactic acidosis (LA). Previous reports have indicated PG-induced LA following PB continuous infusion (CI), but there are no reports in young children. A 3-year-old male was admitted for new-onset seizures. After failing conventional therapy, he was initiated on intravenous PB on hospital day (HD) 3. The seizures continued, and he was initiated on a PB CI on HD 5 to achieve burst suppression. His CI was titrated to 10 mg/kg/hr. On HD 15, he developed hypotension with a mean arterial pressure (MAP) in the 40's and venous lactate of 3.01 mmol/L (normal range: 0.4–2.0 mmol/L). He received epinephrine, and his PB was decreased to 8 mg/kg/hr. Over the next few weeks, he continued to have subclinical seizures and PB was increased to 10 mg/kg/hr. On HD 37, he developed hypotension with a lactate of 6.28 and osmolar gap of 20.4 mOsm/kg. He received a fluid bolus, sodium bicarbonate, and his PB was decreased to 5 mg/kg/hr. His PB was tapered off, and the decision was made to treat clinical seizures only. The World Health Organization recommends a maximum of 25 mg/kg of PG. On HD 15 and 37, our patient received more than this threshold, 1398 and 1604 mg/kg, respectively. The Naranjo probability scale supports a high-probable drug-related adverse event. Practitioners should be aware of this potential adverse event with medications containing PG. Routine monitoring of osmolar gap should be performed for patients with prolonged use or higher PB doses.

Keywords: Pentobarbital, propylene glycol, children, lactic acidosis, pediatrics

1. Introduction

Propylene glycol (PG) is used as a solvent and antimicrobial preservative in the formulation of many

intravenous (IV) medications. High concentrations of PG are found in IV formulations of phenytoin, diazepam, chlorthalidone, etomidate, phenobarbital, pentobarbital, and lorazepam. Pentobarbital IV solution contains 40% volume/volume (v/v) of PG [1]. The World Health Organization recommends a maximum daily intake of 25 mg/kg of PG [2]. Exceeding this amount can result in potentially fatal adverse effects including lactic acidosis and acute kidney injury.

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Several case reports describe patients with presumed PG toxicity, primarily due to lorazepam continuous infusion [3–11]. Two case reports in an adult and adolescent suggest probable PG-induced adverse effects due to continuous infusions of pentobarbital [12, 13]. However, no reports have described this adverse event in a young child.

We report our experience with a pediatric patient receiving a pentobarbital continuous infusion who developed PG-induced lactic acidosis.

2. Case report

A 3-year-old, 17.6 kg Hispanic male was admitted with new onset seizures. He was born via spontaneous vaginal delivery at 37 wk gestation due to preeclampsia, but was otherwise healthy and had no family history of seizures. Five days prior to admission, he developed nasal congestion, a sore throat, and cough. He was seen by his primary care physician and given a prescription for amoxicillin 2 days prior to admission. On the night before admission, he awoke in the middle of the night with fever and headache, which his mother treated with ibuprofen. Per caregiver report, the next morning he vomited and began seizing, with decreased muscle tone, followed by stiffness and right eye deviation. He became unresponsive, and his mother called the paramedics.

En route to the emergency department, he reportedly had three seizures and on arrival exhibited left-sided posturing with right eye deviation. He was given two 0.17 mg/kg doses of IV lorazepam, 45 mg/kg of IV levetiracetam, 17 mg/kg of IV fosphenytoin, and two 0.9% sodium chloride boluses. Following the administration of lorazepam, he developed respiratory depression, was intubated, and was placed on mechanical ventilation. Laboratory blood tests were drawn, and pertinent results are shown in Table 1. A complete urine drug screen was ordered, but was only positive for benzodiazepines. There were no signs of infection as demonstrated by blood, cerebrospinal fluid, and urine cultures. An electroencephalography (EEG) revealed that he was not in subclinical status epilepticus. He underwent a computed topography scan that was reported to be normal, and was subsequently transferred to the pediatric intensive care unit for further management.

He was continued on maintenance doses of IV levetiracetam 27.6 mg/kg every 12 hr, fosphenytoin 1.3 mg/kg every 8 hr, and PRN IV lorazepam 0.05 mg/kg

Table 1
Chemistry values on admission to the pediatric intensive care unit

Parameter (reference range)	Patient result
Sodium (134–144 mEq/L)	137
Potassium (3.5–5.1 mEq/L)	4.3
Chloride (96–108 mEq/L)	106
Serum bicarbonate (22–30 mEq/L)	24
Blood urea nitrogen (7–18 mg/dL)	11
Creatinine (0.20–0.70 mg/dL)	0.36
Glucose (65–110 mg/dL)	305
Calcium (8.8–10.8 mg/dL)	8.5
Aspartate aminotransferase (15–60 U/L)	73
Alanine aminotransferase (10–45 U/L)	28
Total protein (6.1–7.4 g/dL)	6.9
Albumin (3.4–5.2 g/dL)	4.0

every 2 hr for seizures. He continued to have both clinical and electrographic subclinical seizures, prompting the use of continuous EEG monitoring and an increase in his maintenance dose of IV levetiracetam to 32.2 mg/kg every 12 hr. On hospital day (HD) 3, a midazolam continuous infusion (CI) and IV lacosamide 3.75 mg/kg every 12 hr was initiated. In addition, he was loaded with phenobarbital 20 mg/kg IV, followed by maintenance dose of 5 mg/kg/dose every 12 hr. The patient continued to have subclinical seizures, and on HD 5, a pentobarbital CI was started at 1 mg/kg/hr to achieve burst suppression. His maintenance phenobarbital was discontinued on HD 9. On HD 11, topiramate 150 mg twice daily given via transpyloric feeding tube was added to his seizure regimen.

During HD 5–15, he continued to have subclinical seizures, and his pentobarbital CI was increased with additional pentobarbital bolus doses as needed. On HD 15, the patient developed hypotension with a mean arterial pressure (MAP) in the 40's as well as an elevated serum lactic acid concentration. Table 2 shows laboratory values and other pertinent details for the days surrounding the patient's first episode of lactic acidosis. At this time, his pentobarbital CI rate was 10 mg/kg/hr. To treat his hypotension, he was initiated on an epinephrine CI, and the pentobarbital CI was decreased to 8 mg/kg/hr.

On HD 17–39, he continued to have subclinical seizures, and was re-initiated on IV phenobarbital 2.9 mg/kg every 12 hr on HD 17. His pentobarbital CI was increased to achieve burst suppression due to the number of subclinical seizures noted on his EEG. On HD 37, the patient again developed hypotension and lactic acidosis. Table 3 includes laboratory values and other pertinent details for the patient's second episode

Table 2
Clinical details for first episode of propylene glycol toxicity

Parameter (reference range)	Hospital day 13	Hospital day 14	Hospital day 15	Hospital day 16	Hospital day 17
Pentobarbital dose (mg/kg/hr)	7.5	10	10	5	2
Propylene glycol dose (mg/kg)	1677	1985	1398	640	249
Serum bicarbonate (22–30 mEq/L)	21	21	18	17	16
Anion gap (4–14 mEq/L)	10	12	9	7	11
Venous pH (7.38–7.44)	7.40	7.44	7.39	7.29	7.23
Venous lactate (0.4–2.0 mmol/L)	–	–	3.01	–	–

Table 3
Clinical details for second episode of propylene glycol toxicity

Parameter (reference range)	Hospital day 35	Hospital day 36	Hospital day 37	Hospital day 38	Hospital day 39
Pentobarbital dose (mg/kg/hr)	8	9	9	5	4
Propylene glycol dose (mg/kg)	2044	2151	1604	1025	565
Serum bicarbonate (22–30 mEq/L)	16	24	22	19	16
Anion gap (4–14 mEq/L)	10	4	8	8	8
Venous pH (7.38–7.44)	7.23	7.37	7.35	7.37	7.36
Venous lactate (0.4–2.0 mmol/L)	–	–	6.28	1.46	–
Osmolar gap (<10 mOsm/kg)	–	–	20.04	–	–

Table 4
Total propylene glycol exposure

Medications received with propylene glycol	Hospital day received	Propylene glycol (mg)	Propylene glycol (mg/kg)
Lorazepam	3.40–41	673.9	38.2
Phenobarbital	3–9, 17–39	66,285.9	3766
Pentobarbital	5–41	75,2557.2	42,759
Cumulative propylene glycol from all sources	Not available	81,9517	46,563
Mean daily propylene glycol on hospital day 5–41	Not available	22,149.1	1258

of lactic acidosis. At this time, his pentobarbital CI rate was 9 mg/kg/hr. Of note, his daily intake of PG peaked on HD 36 at 2151 mg/kg with 96% of this exposure secondary to pentobarbital CI and the remainder attributed to phenobarbital IV. The resulting serum lactate concentration was 6.28 mmol/L. In response to his lactic acidosis, the patient was given a bolus of Lactated Ringer's, a dose of IV sodium bicarbonate, and was initiated on a dopamine CI. His pentobarbital CI was again decreased back to 5 mg/kg/hr. On HD 41, after consultation with pediatric neurology and his family, the decision was to only treat clinical seizures. At this time, his pentobarbital CI and continuous EEG monitoring were discontinued.

The patient continued to have clinical seizures for the remainder of his hospital stay. After a thorough work-up of potential etiologies of his new-onset seizures, it was determined that his refractory status epilepticus was likely post-infectious in origin. He was successfully extubated on HD 64, and was discharged home on HD 91. At discharge, the patient continued to have constant myoclonic seizures with oxygen desaturations in the 80's which spontaneously recovered. His

discharge medications included levetiracetam 660 mg every 12 hr per nasogastric tube (NG), valproic acid 40 mg every 8 hr NG, and diazepam 0.5 mg every 12 hr NG. The patient was discharged home in the care of his parents with plans to follow-up for outpatient care at a local pediatric rehabilitation facility.

3. Discussion

To our knowledge, this is the first report of PG-induced LA in a young child attributed to a pentobarbital CI. There is a paucity of data regarding this adverse effect in pediatric patients receiving IV pentobarbital. Two previous case reports have correlated use of pentobarbital continuous infusions to PG-induced LA and other serious adverse events such as serum hyperosmolality, elevated serum creatinine concentrations, and acute kidney injury (AKI) [12, 13].

Yorgin et al. [12] reported a case of a 16-year-old male with tonic-clonic seizures who developed PG-induced serum hyperosmolality, lactic acidosis and AKI after receiving pentobarbital CI and phenobarbital

IV, both of which contain significant amounts of PG [12]. This patient's peak pentobarbital CI dose on the day prior to development of the PG-induced toxicity was 4 mg/kg/hr, and his phenobarbital IV dose was 6.7 g. Their cumulative PG exposure was approximately 8116 mg/kg from phenobarbital and pentobarbital. As the patient received significant exposure to both agents, it is difficult to ascertain which medication was the primary contributor to the PG-induced toxicity. Approximately 60% of PG exposure on the day prior to development of the PG-induced AKI and lactic acidosis was secondary to the pentobarbital CI.

One other report describes the development of PG-induced lactic acidosis secondary to a pentobarbital CI in an adult patient [13]. This patient was a 59-year-old female with refractory status epilepticus. Her pentobarbital CI was initiated at 0.5 mg/kg/hr, and the dose was doubled every hour until she achieved burst suppression as noted on the EEG. Twelve hour after the infusion was initiated; she developed a lactic acidosis with a serum lactate of 13.2 mEq/L. At this time, her pentobarbital CI dose was 10 mg/kg/hr. Her cumulative PG dose prior to this event was 1930 mg/kg. A complete list of concomitant medications was not provided, so it is difficult to determine if there were any other contributors to PG-induced toxicity.

Our patient received multiple PG-containing medications including a pentobarbital CI, maintenance phenobarbital IV, and as needed lorazepam IV (Table 4). Compared to the case report by Yorgin et al. [12], our patient received a significantly higher peak pentobarbital dose around the time of development of the first and second PG-induced LA episodes, 9 and 10 mg/kg/hr, respectively. In contrast to the report by Miller et al. [13], our patient received approximately the same peak infusion dose but developed the PG-induced toxicity within a shorter time frame. This was likely due to the rapid titration schedule with the pentobarbital CI. Our patient had a significantly higher cumulative exposure 46,563 mg/kg, which is approximately six times as much PG than reported by Yorgin et al. [12], and significantly higher than the World Health Organization recommendations of 25 mg/kg/day [12]. The total PG exposure was not reported by Miller et al. [13], so it is difficult to make a comparison to our patient.

In these previous cases reports, the authors describe the use of monitoring to confirm the suspicion of PG-induced toxicity [12, 13]. In both reports, they

obtained serum PG concentrations and obtained a serum osmolality concentration to calculate an osmolar gap. The PG concentrations noted in the report by Yorgin et al. [12] were 4.1–21 mg/dL and osmolar gap was 22.2–27.4 mOsm/kg. However, it should be noted that these concentrations were obtained approximately 5 days after the first signs of toxicity, so it is not an accurate reflection of these markers during the initial signs of toxicity [12]. In contrast, Miller et al. [13], obtained PG concentrations while the patient was on the peak dose of 10 mg/kg/hr and 5 mg/kg/hr, and they were found to be 170 and 140 mg/dL, respectively. They also found an osmolar gap of 34–43 mOsm/kg around the time of the event.

In our patient, we did not obtain PG concentrations. However, with the second episode of PG-induced metabolic acidosis, we did obtain a serum osmolality and calculated an osmolar gap that was 20.4 mOsm/kg. Osmolar gap has been demonstrated to be the strongest predictor of serum PG concentrations ($r = 0.804$, $P = 0.001$) in a report by Arroliga et al. [4]. Even though we did not obtain PG concentrations and perform an osmolar gap with both episodes, there were no other potential explanations for the metabolic acidosis with either episode. The episodes also resolved upon a reduction in the pentobarbital dose. In addition, the patient had the same response when their pentobarbital dose was increased back up to 9 mg/kg/hr. To confirm our suspicion, we utilized the Naranjo et al. [14] probability scale and determined a high probability (> 9) of a drug-related adverse event in our patient.

The majority of the reports regarding PG-induced adverse effects involve adults and children receiving CI lorazepam [3–11]. Clinicians may be unaware of the possibility of PG toxicity when ordering other medications such as phenytoin, phenobarbital, and pentobarbital. It is important to be vigilant for signs and symptoms of PG toxicity to prevent further complications. There is a paucity data regarding the best management of these patients once PG-induced toxicity occurs. Zosel et al. [9] reported using IV fomepizole and hemodialysis to treat a 50-year-old male with an iatrogenic overdose of IV lorazepam that resulted in decreased serum PG-concentrations. Hemodialysis was also described to substantially reduce serum PG concentrations in a 34-year-old patient with lactic acidosis after receiving high doses of lorazepam CI [10]. In many cases, decreasing the dose of medications containing PG will improve lactic acidosis without other interventions.

A reasonable approach to identifying patients at risk for developing PG toxicity with pentobarbital CI includes targeting specific patient factors. These factors include children with renal dysfunction (i.e., creatinine clearance less than 30 mL/min/1.73 m²), concomitant use of other scheduled medications containing PG (e.g., lorazepam CI, phenobarbital IV, phenytoin IV), pentobarbital CI dose greater than 4 mg/kg/hr, expected duration greater than 3 days, and neonatal patients due to decreased renal clearance of PG. Patients with one or more of these specific factors should have a serum osmolality obtained every other day to calculate an osmolar gap. Consideration of a dose reduction or discontinuation of the pentobarbital CI should occur if the osmolar gap is > 10 mOsm/kg and signs of symptoms of toxicity are present. PG concentrations could also be obtained for confirmation of toxicity. However, this laboratory value is a send out test and may not be readily available to guide the decision making process.

In conclusion, this case report provides a description of a critically-ill child who developed PG-induced lactic acidosis after receiving a high-dose pentobarbital CI. PG-related adverse effects are well-described in the literature in patients receiving lorazepam, but many clinicians may be unaware that toxicity can occur with other agents including phenytoin, phenobarbital, and pentobarbital. Children receiving pentobarbital CI with specific risk factors should have a serum osmolality monitored every other day to calculate an osmolar gap in order to more rapidly identify the potential of toxicity and adverse events.

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