CASE REPORT

Pentobarbital-induced lactic acidosis following status epilepticus barbiturate coma

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SUMMARY

We present a rare case of pentobarbital infusion causing propylene glycol-induced lactic acidosis, during refractory status epilepticus treatment in a 66-year-old man without seizure history.

BACKGROUND

Propylene glycol (1,2-propanediol; PG) is a commonly used organic pharmaceutical solvent and carrier molecule with low toxicity, most often reported with its use in high doses of intravenous benzodiazepines, particularly lorazepam.^{1–5} Continuous infusion of medications containing PG can lead to its accumulation causing toxicity, with osmol and anion gap metabolic acidosis in addition to other serious adverse effects including central nervous system depression, seizures, intravascular haemolysis, cardiac arrhythmias, respiratory arrest and renal failure.⁶ We present a rare case of pentobarbital infusion causing PG-induced lactic acidosis during refractory status epilepticus treatment.

CASE PRESENTATION

A 66-year-old man with medical history significant for alcoholic cirrhosis, essential tremor and without seizure history was found unresponsive with a pulse and normal glucose level. In the emergency department, tonic-clonic activity began, resolving following 0.5 then 1.5 mg lorazepam administration. Low-dose propofol and fentanyl infusions were started following intubation. Head CT without contrast demonstrated no acute intracranial abnormalities. Electrolytes, glucose, troponin, and ethanol and urine toxicology were normal. Urine culture grew *Escherichia coli* later during admission. At that time, he was started on vancomycin, ceftriaxone, ampicillin and acyclovir for suspected meningitis. However, lumbar puncture was later negative, although performed following a first dose of antibiotics. On admission, lactic acid was 3.4 mmol/L and resolved with fluid resuscitation. He was started on levetiracetam; however, all extremities continued twitching intermittently. While off sedation, after briefly on propofol for intubation, he opened his eyes to sternal rub and exhibited purposeful movements, but did not follow commands. Cranial nerve reflexes were grossly intact and intention tremor noted, 2+ DTR throughout, plantar reflex mute. Intravenous levetiracetam was given 750 mg twice daily following 1500 mg loading. Spot/30 min EEG performed on day 2 showed continued seizure activity. He was transitioned from

propofol to midazolam after a hypotensive episode and titrated to burst suppression, with a goal of burst suppression for 24 hours. Intravenous phenytoin (which also contains PG) 100 mg every 8 hours after loading dose was added. Repeat continuous EEG showed evidence of subclinical status epilepticus. Due to inadequate burst suppression, a pentobarbital infusion to induce coma was administered, with the goal to titrate down once complete burst suppression or burst with long periods of suppression was achieved for 24 hours (pentobarbital: 5 mg/kg bolus, 1 mg/kg/hour continuous for 24 hours and 0.5 mg/kg/hour for the following 24 hours; a cumulative dose of 36.1 mg/kg of pentobarbital over 48 hours). He achieved complete burst suppression with this regimen, but increased lactic acid was noted after starting pentobarbital, peaking at 6.0 mmol/L over the next 24 hours. Since he had complete suppression for 24 hours, pentobarbital was discontinued, and his lactic acid dropped to 3.4 mmol/L 4 hours after pentobarbital discontinuation and then to 1.9 mmol/L (normal) the next day.

INVESTIGATIONS

A brain MRI with and without gadolinium contrast was performed using the seizure protocol, which found no evidence of acute intracranial abnormality; and follow-up brain MRI was unchanged.

DIFFERENTIAL DIAGNOSIS

PG toxicity classically presents with an anion and osmol gap metabolic acidosis associated with haemodynamic lability, renal insufficiency and, if untreated, multiorgan system dysfunction.⁷ Distinguishing PG toxicity from sepsis and systemic inflammatory response syndrome can be difficult.⁸ Measurement of serum osmolality or a PG level can help distinguish the two entities. In addition to PG-containing medications, other causes of metabolic acidosis should be considered. Also, status epilepticus itself has been associated with severe metabolic acidosis.⁹ PG toxicity may actually induce complications that barbiturates are intended to treat, including seizures and elevated intracranial pressure.^{10 11}

TREATMENT

Discontinuation of offending agent.

OUTCOME AND FOLLOW-UP

Family elected to transition care to comfort care and patient deceased few days after transition to hospice.

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DISCUSSION

Pentobarbital, effective in treating refractory status epilepticus, comprised 40% by volume of PG, an organic, colourless, odourless, sweet tasting, non-ionic, highly water-soluble excipient used in numerous pharmaceutical agents including oral, intravenous and topical preparations. PG, a small molecular weight alcohol (76.1 Da), is considered safe (GRAS by the US Food and Drug Administration, 21 CFR 184.1666); however, risk of toxicity increases when given in frequent and prolonged doses, and it is associated with a high anion gap metabolic acidosis (as it is hyperosmolar), which can be lethal if untreated.⁸ Despite the food additive maximum of 25 mg/kg/day of PG established by WHO, there is no recommended maximum intravenous dose in the USA.

PG toxicity is an iatrogenic complication that can be life threatening but has not been well studied. The mechanism of PG toxicity is unknown^{2,5}; however, in vitro studies suggest that PG itself is cytotoxic to the renal proximal tubular cells.^{12–14} Toxicity has been associated with serum PG concentrations >18–25 mg/dL, metabolic abnormalities at 58–127 mg/dL and clinical deterioration at 104–144 mg/dL.^{5,15–18} Hepatic or renal impairment increase toxicity risk due to PG metabolism via hepatic alcohol and aldehyde dehydrogenase (~55%) and 30%–45% renal excretion.^{19,20} Ethanol abuse has been speculated to increase susceptibility to PG toxicity, as similar enzyme pathways metabolise both compounds leading to a high anion gap metabolic acidosis.

The osmolar gap, anion gap and lactate are commonly elevated in PG intoxication. Definitive diagnosis requires serum PG level, a test sent out to a specialty laboratory by most institutions, which may delay diagnosis. Osmol gap has been suggested as a more useful surrogate measurement given the relative speed at which an osmol gap can be obtained relative to PG level.^{2,17,21–23} An osmolar gap at 48 hours is considered the strongest predictor of PG concentration while an elevated anion gap and lactic acidosis are poor indicators.^{2,5,17} The estimated osmolar effect of PG can be calculated by dividing the PG level by 7.6.²¹

Although PG toxicity is increasingly recognised and reported, its incidence is unknown. Likewise, a normal or acceptable level of PG has not been defined, making the clinical implication of PG levels uncertain.⁵ Studies over the past 10 years highlight a growing interest in PG toxicity; however, few reports relate to its use in pentobarbital, with most reports relating to its use as a vehicle in lorazepam and etomidate.^{24–27} Close monitoring of the osmolar gap, a reasonable surrogate for PG accumulation, in patients receiving intravenous pentobarbital is warranted for early evidence of PG toxicity.

Learning points

- ▶ When a patient receives large doses of propylene glycol containing medications, propylene glycol toxicity should be considered as a potentially life-threatening iatrogenic complication.
- ▶ Propylene glycol toxicity classically presents with an anion and osmol gap metabolic acidosis.
- ▶ Close monitoring of the osmolar gap and lactic acid in patients receiving intravenous pentobarbital or other propylene glycol containing medications is warranted to detect propylene glycol toxicity.

Contributors TRG helped in writing the discussion of this case report. VS: neurology resident was caring for the patient, helped in writing the neurological

findings and medications administrations, RW: literature review and writing the abstract. SG: direct patient care and wrote the case presentation.

Competing interests None declared.

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