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CASE REPORT

Unexplained Metabolic Acidosis: Alcoholic Ketoacidosis or Propylene Glycol Toxicity

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Abstract

Introduction Severe metabolic acidosis with elevated anion and osmol gap is suggestive of toxic alcohol ingestion. The absence of detectable methanol or ethylene glycol in the serum could mean that metabolism is complete or that other hypotheses have to be considered. Ingestion of less common alcohol or alcoholic ketoacidosis should be investigated as illustrated by the present observation.

Case Report A 46-year-old woman was admitted with altered consciousness in the Emergency Department. In the presence of a high anion gap (peak value 39 mEq/L) metabolic acidosis with mildly increased osmol gap (peak value 19 mOsm/kg), there was a high suspicion of toxic alcohol ingestion in an individual with alcohol use disorder (AUD). Serum arterial lactate concentration was particularly high at 27 mmol/L. Urinalysis failed to reveal the presence of ketone bodies or oxalate crystals. The results of the serum determination of ethanol, methanol, ethylene glycol, and isopropanol were obtained within 2 h and were negative. Due to the severity of lactic metabolic acidosis and the persisting suspicion of intoxication by a less common toxic alcohol, antidotal therapy with ethanol was initiated together with hemodialysis. Correction of lactic metabolic acidosis was obtained. Results of urinalysis obtained later revealed the presence not only of propylene glycol and D-lactate but also of significant concentrations of ß-hydroxybutyrate as a marker of alcoholic ketoacidosis.

Discussion The combination of propylene glycol ingestion and alcoholic ketoacidosis may have contributed to the severity of lactic acidosis.

Keywords Alcoholic ketoacidosis · Propylene glycol ingestion · Lactic acidosis · L,D-lactate · Hemodialysis · Antidote

Introduction

Among toxic alcohols, voluntary or accidental ingestion of methanol or ethylene glycol is frequently reported among individuals with AUD. The diagnosis is often based on the evidence of severe metabolic acidosis with a high anion gap and high osmolal gap values. Gas chromatography usually allows the confirmation of the presence of methanol or ethylene glycol. The detection of less common toxic alcohols (di- or triethylene glycol, propylene glycol) is not routinely available in many facilities [1]. This could delay supportive or specific therapy. Among confounding factors, alcoholic ketoacidosis must also be considered [2]. We describe a case of initially unexplained metabolic acidosis requiring intensive care admission for hemodialysis and antidote.

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Case Report

A 46-year-old woman was admitted to the emergency department (ED) with altered consciousness. She had a history of AUD. She had been found stuporous at home in her armchair, with a large bleeding wound of the scalp. She was confused and not able to record the events of the last hours. The husband suspected a new episode of ethanol abuse. On arrival in the ED, vital signs were: Glasgow Coma Scale (GCS) score 14/15 (E4, V4, and M6), temperature 34.5 °C, heart rate 120/min, arterial blood pressure 75/50 mmHg, and respiratory rate 32/min.

Relevant laboratory investigations were: serum glucose 40 mg/dL [70–100], arterial pH 6.95 [7.35–7.45], pCO_2 16 mmHg [35–45], total bicarbonate 6 mEq/L [22–28], lactate 27 mmol/L [0.50–2.2], serum osmolality 306 mOsm/kg [280–300], creatinine 2.80 mg/dL [0.60–1.30], haemoglobin 6.0 g/L [12.2–15.0], haptoglobin 0.21 mg/dL [0.30–2.00], total bilirubin 2.3 mg/dL [< 1.2], and INR 1.68 [0.80–1.20]. To exclude interferences in lactate determination, a later serum sample was analyzed by three different methods, two enzymatic and one colorimetric: Radiometer ABL800 (L-lactate oxidase assay), Roche Cobas analyzer (L-lactate oxidase assay as well), and L-lactate dehydrogenase manual colorimetric assay. The results obtained were 14.3, 15.2, and 18.0 mmol/L, respectively. D-lactate level was 0.8 mmol/L. The calculated anion gap was 37 mEq/L, and the osmol gap was 12 mOsm/kg. These results were suggestive of toxic alcohol ingestion. However, blood tests for ethanol, isopropanol, methanol, and ethylene glycol screening were all negative. Oxalate crystals were not found in the urine, and ketone bodies were also absent. Glycolate concentration in the urine was 10.8 mmol/mmol creatinine (reference < 37), acetoacetate 3.2 mmol/mmol creatinine (< 5), 3(ß)-hydroxybutyrate 227.5 mmol/mmol creatinine (< 15), lactate (L + D) 1662.2 mmol/mmol creatinine (< 100), D-lactate 549.6 mmol/mol creatinine (< 0.03), and pyruvate 102.3 mmol/mmol creatinine (< 20). Nevertheless, as these last results were not immediately available, it was decided to start antidotal therapy with intravenous ethanol. After a loading dose of 0.6 g/kg, 150–250 mg/kg/h was infused with a target ethanol level of 100 mg/dL. The total duration of ethanol therapy was 19 h. Symptomatic therapy also included bicarbonate administration. Despite thiamine administration and fluid therapy, severe metabolic acidosis with oliguria persisted, and hemodialysis was then initiated (two courses: day 1 from 10:00 p.m. to day 2 0:00 a.m., day 2 from 12:00 p.m. to 04:00 p.m.). Further evolution of laboratory results is shown in Table 1. Renal function recovered rapidly. The presence of propylene glycol (108 mg/L) was documented retrospectively on the admission urine sample (headspace concentration gas chromatography coupled with mass spectrometry detection; HS-GC–MS), but not in the serum. The source of propylene glycol could never be definitely identified. Possible sources were cosmetics or propylene glycol containing antifreeze as her husband, as a farmer, used several agricultural machines. The patient never received any propylene glycol-containing medication.

Liver ultrasonography revealed a diffuse increase in echogenicity of the liver parenchyma and nodular liver surface. Liver cirrhosis was graded A according to the Child–Pugh classification. The patient developed as delayed complication

Table 1 Evolution of laboratory values

	Day 14:00 p.m	Day 1 7:00 p.m	Day 1 8:00 p.m	Day 1 10:00 p.m	Day 2 0:30 a.m	Day 2 4:00 a.m	Day 2 8:00 a.m	Day 2 12:00 a.m
Arterial pH *(7.35–7.45)*	6.95	7.16	7.21	7.36	7.45	7.39	7.37	7.41
Serum bicarbonate (mEq/L) *(22–28)*	6	6	7	14	20	14	14	20
Anion gap (mEq/L) *(8–12)*	37	39	32	20	-	9	19	15
Serum osmolality (mOsm/kg) *(280–300)*	306	310	-	-	-	310	-	-
Osmol gap (mOsm/kg)	12	19	-	-	-	36 (2**)	-	-
Urine ketone bodies	Absent	-	-	-	-	-	-	-
Urine 3(ß)-hydroxybutyrate (mmol/mmol creatinine)	227.5	-	-	-	-	-	-	-
Urine propylene glycol (mg/L)	108	-	-	-	-	-	-	-
Serum ethanol (mg/dL)	0	0	-	80	50	130	-	-
Serum methanol or ethylene glycol (mg/dL)	0	-	-	-	-	-	-	-
Serum L-lactate (mmol/L)* *(0.5–2.0)*	27	25	19	11.7	6.8	10.8	10.0	5.8
Serum creatinine (mg/dL) *(0.6–1.30)*	2.80	-	-	0.89	-	0.79	-	-

*determined on Radiometer ABL 800

**adjusted for a serum ethanol level of 130 mg/dL

a post-traumatic left frontotemporal intraparenchymal hematoma with right-sided hemiparesia.

Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Discussion

The presence of a high anion gap metabolic acidosis together with an increased osmol gap raised the suspicion of toxic alcohol ingestion, namely methanol, ethylene glycol, or any other glycol. Recent ingestion of isopropanol causes an increased osmol gap, while its metabolism does not produce acidic metabolites, but well acetone. The absence of detectable methanol, ethylene glycol, or isopropanol in the serum could mean that the metabolism is already complete or that other hypotheses have to be considered. An alternative diagnosis could be alcoholic ketoacidosis (AKA) in a chronic ethanol abuser (see Table 2 for differential diagnosis [2]) [3]. Measured lactate concentrations in the setting of AKA are usually < 10 mmol/L, but higher values were occasionally reported [3]. The possibility of an increased osmol gap in AKA has been addressed by several publications [3, 4]. The pathophysiology of the increased osmol gap in AKA is not precisely known, and the exact contribution of acetone is debated [4]. The absence of ketone bodies at urine point of care dipstick tests does not exclude the presence of AKA [3]. The accessibility of serum or urine testing for acetoacetate and ß-hydroxybutyrate is usually limited. In the present observation, the results of urine lactate, pyruvate, and ß-hydroxybutyrate concentrations were obtained with delay, but at least suggested that AKA was involved in the genesis of metabolic acidosis.

Unexpectedly, propylene glycol was detected retrospectively in the urine sampled at admission. Together with the production of L-lactate and D-lactate, this supports the likelihood of propylene glycol toxicity. Propylene glycol (PG) or 1,2 propanediol is an organic solvent often used as a preservative in cosmetics, processed food, e-cigarettes, and oral, topical, or injectable medications, and also as an antifreeze replacement for ethylene glycol [5]. In comparison with ethylene glycol or methanol poisoning, intoxication by PG ingestion is unusual in humans and PG appears less toxic [6]. The majority of the cases with toxic reactions were reported following the accumulation of PG used as an excipient for intravenous medications [7]. Massive PG poisoning (mostly after intravenous route) has caused reversible central nervous system abnormalities, including altered consciousness, seizures, or nystagmus. Hemolysis and kidney failure are other possible complications. In the present observation, the transient increase in serum creatinine may be due to dehydration or to some interference of ketone bodies with creatinine measurement [8]. In mammals, PG is metabolized via the same metabolic pathway as ethanol, ethylene glycol, or methanol [9]. It is converted to D,L-lactaldehyde, and then L-lactate under the influence of, respectively, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) (Fig. 1). Possible interference exists between PG (or derived metabolites) and L-lactate measurement with some arterial blood gas analyzers (including Radiometer ABL800) when the method is based on glucose oxidase assay [10]. There is an alternative pathway leading to the production of methylglyoxal transformed to D-lactate via glyoxalase. In a case of massive accidental ingestion of PG with high anion gap metabolic acidosis, Jorens et al. found high amounts (up to 110 mmol/L) of D-lactate in the serum [10]. The hypothesis was the conversion of ingested PG into D-lactate by intestinal bacteria. The determination of PG in plasma and urine by gas–liquid chromatography is usually not available on a routine base in most hospital laboratories. Therefore, the diagnosis of PG poisoning is often obtained retrospectively. Theoretically, the metabolism of PG may be inhibited by the blockade of ADH, based on limited clinical evidence as the direct toxicity of PG appears to be low. Fomepizole most likely blocks ADH metabolism of PG effectively, but clinical evidence for this is limited [11]. The alternative is the administration of intravenous ethanol as a competitive inhibitor of ADH, with the same dosage regimen as for other

Table 2 Differential diagnosis according to arterial pH, anion gap, osmol gap, and ketone bodies. For contribution to osmol gap, toxin concentration is expressed in mg/dL. The values of anion and osmol gap are influenced by the delay from exposure. *Estimation of contribution of propylene glycol (PG) concentration to osmol gap in patients receiving lorazepam infusions: [PG] mg/dL = 14.22 + 1.94*osmol gap [Ref 2]. (Adapted from https://www.healthcare.uiowa.edu/path_handbook/Appendix/Chem/OSMO_GAP.html, accessed Dec 12, 2021)

	Arterial pH	Anion gap	Ketone	Osmol gap	Contribution to osmol gap
Ethanol	Nl	Nl	Nl	↑	[Ethanol]/3.8
Methanol	↓	↑	Nl	↑ or Nl	[Methanol]/3.2
Ethylene glycol	↓	↑	Nl	↑ or Nl	[Ethylene glycol]/6.2
Isopropanol	Nl	Nl	↑	↑	[Isopropanol]/6.0
Propylene glycol	↓	↑	Nl	↑ or Nl	[Propylene glycol]/2.8*
Alcoholic ketoacidosis	↓	↑	↑	↑	Contribution of acetone debated [3]

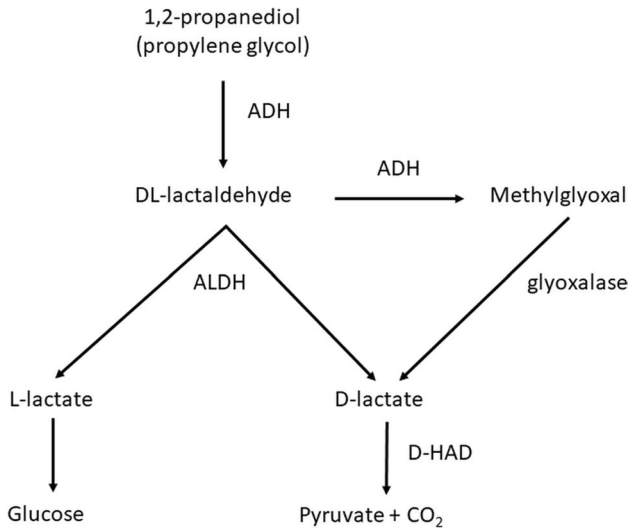

Fig. 1 Metabolic pathway of 1,2-propanediol (propylene glycol). *ADH*, alcohol dehydrogenase; *ALDH*, aldehyde dehydrogenase; *D-HAD*, D-2-hydroxyacid dehydrogenase

toxic alcohols poisoning [5]. Propylene glycol, like ethylene glycol or methanol, is dialyzable [12]. Hemodialysis is indicated in the presence of renal failure, severe metabolic acidosis, or extremely high PG serum levels.

The main limitation of this observation is the absence of definitive identification of the propylene glycol source. The patient made a slow neurological recovery after post-traumatic brain hematoma and could never remember the circumstances of poisoning. A domestic source appears likely (cosmetics or propylene glycol containing antifreeze).

This case illustrates the difficulty of distinguishing between toxic alcohol ingestion versus AKA in some patients presenting for emergency care. In many hospitals, not only toxic alcohols but also ß-hydroxybutyrate concentrations are not available in a clinically relevant timeframe. This could influence medical-decision making and particularly the use of antidotes and hemodialysis.

Declarations

Consent for Publication Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Potential Conflicts of Interest None.

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