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CLINICAL QUIZ

Metabolic acidosis with increased anion gap, oxaluria, and acute kidney injury: Answers

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Answers

(1) What is the most likely cause of acute kidney injury?

The patient in this case had somnolence, metabolic acidosis with increased anion gap, oxaluria, and steadily increasing serum creatinine. Based on laboratory findings, intoxication was initially suspected. Salicylate, barbiturate, methanol, and ethylene glycol (EG) poisoning were considered in differential diagnosis. The parents were questioned about the patient's alcohol and drug history and psychological state (suicidal tendency) but no helpful information was obtained. The urine drug screen was negative, and a toxicology screen of the serum identified no heroin, cocaine, amphetamine or methamphetamine. Eventually, the patient's friend called his father to report that the patient had recreationally drunk antifreeze at work several days prior, confirming our preliminary diagnosis of EG poisoning.

(2) Which additional tests would you perform to confirm the diagnosis?

Serum EG concentration can be checked to confirm the diagnosis. The patient's serum EG level was above 200 mg/L. The diagnosis and therapy guidelines for EG poisoning have been developed by the American Academy of Clinical Toxicology (Table 1) [1].

(3) How should this patient be treated?

The initial approach in EG poisoning includes stabilization of the airway, breathing, circulation, and supportive therapy. The main goals in treating EG poisoning are prevention of toxic metabolite formation, infusion of bicarbonate for acidosis, use of specific enzymatic cofactors such as thiamine and pyridoxine, and removal of the toxins and metabolites by hemodialysis [2].

In our case, bicarbonate infusion was initiated to correct acidosis after the first evaluation. Serum creatinine steadily

Table 1 Criteria for antidotal therapy in ethylene glycol poisonings (1)

- Serum ethylene glycol concentration > 200 mg/L (3 mmol/L) or
- Patient history of ingestion of a toxic dose of ethylene glycol and osmotic gap of more than 10 mOsmol/kg or
- Suspicion of ethylene glycol poisoning by history, or clinical signs and symptoms and two of the following criteria:

1. Arterial pH < 7.3
2. Serum bicarbonate < 20 mmol/L
3. Osmotic gap > 10 mOsmol/kg
4. Calcium oxalate crystals in urine sediment

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increased from 1.2 to 6.7 mg/dL. Hemodialysis and empirical intravenous antidote treatment with ethanol were started (0.6 g/kg within 60 min, followed by 0.1 g/kg/h). Thiamine (100 mg) and pyridoxine (100 mg) were given intravenously as a single dose. Amlodipine and atenolol were started orally as antihypertensive therapy. The patient's serum EG level was at > 200 mg/L.

The patient was further treated with ethanol and underwent hemodialysis for 3 days for acute kidney injury. Episodes of hypoglycemia were observed repeatedly but there was no significant response to treatment. Fomepizole was not available immediately; the poison control center supplied fomepizole on day 3 of hospitalization. Ethanol infusion was stopped; 15 mg/kg fomepizole was given as loading dose, and 10 mg/kg maintenance dose after 12 h. Serum creatinine subsequently decreased to 2.2 mg/dL and hemodialysis was stopped. The patient's creatinine level decreased to 1.4 mg/dL by the end of day 6. Serum creatinine values according to treatment are given in Fig. 1. At final examination, serum creatinine was 0.9 mg/dL while spot urine protein/creatinine ratio was 0.2 mg/mg.

Pediatric psychiatry consultation revealed no previous history of substance abuse; the patient had drunk the liquid thinking it contained alcohol.

Discussion

Ethylene glycol is an organic compound used for antifreeze formulations and as raw material for polyester production. Due to its lack of color and odor and a sweet taste, it is often ingested by dogs; accidental EG poisoning in humans is rare. Global EG mortality rates are reported at 1–22% [3]. Ethylene glycol is metabolized by alcohol dehydrogenase and other liver enzymes to glycolaldehyde, glycolic acid (GA), and oxalic acid. Toxicity is secondary to GA and oxalic acid. Calcium oxalate crystals can cause acute kidney injury and toxicity in the brain and other organs. The diagnosis of EG poisoning is considered primarily in patients with confusion, metabolic acidosis, serum EG concentration of over 200 mg/L, and an appropriate history.

Diabetic and alcoholic ketoacidosis, uremia, lactic acidosis, and methanol poisoning should be considered [2] in the differential diagnosis.

Ethylene glycol toxicity is divided into 3 distinct phases: central nervous system (CNS) depression (stupor, nausea and vomiting, hallucinations, and seizures), cardio-respiratory toxicity (hypotension, tachypnea, congestive heart failure or, occasionally, myositis), and kidney toxicity (flank pain, oxalate crystalluria, oliguric kidney failure) [1].

Ethylene glycol poisoning was suspected in our patient due to presence of somnolence, metabolic acidosis, acute kidney injury, and oxaluria. IV bicarbonate and fluid infusion, thiamine, and pyridoxine therapy were started. A blood sample was sent to a regional toxicology laboratory for EG analysis. It was decided to start empirical ethanol treatment and hemodialysis based on preliminary diagnosis. Fomepizole can be difficult to acquire as it is not available in every hospital. As the main focus of treatment is the inhibition of glycolic acid production, ethanol and fomepizole are used as an antidote. Ethanol has been used as an efficient and inexpensive antidote for many years, but due to the risk of hypoglycemia and alcohol poisoning and the preservation of therapeutic plasma concentration (500–1000 mg/L), serum ethanol and glucose levels should be checked regularly during ethanol therapy [4]. Our patient had episodes of hypoglycemia, and serum ethanol was extremely difficult to monitor.

Fomepizole is a safe and effective competitive inhibitor of alcohol dehydrogenase that does not require serum concentration monitoring. The most common side effects of fomepizole are headache and nausea [5]. There have been no clinical trials, in adults or children, comparing the efficacy and safety

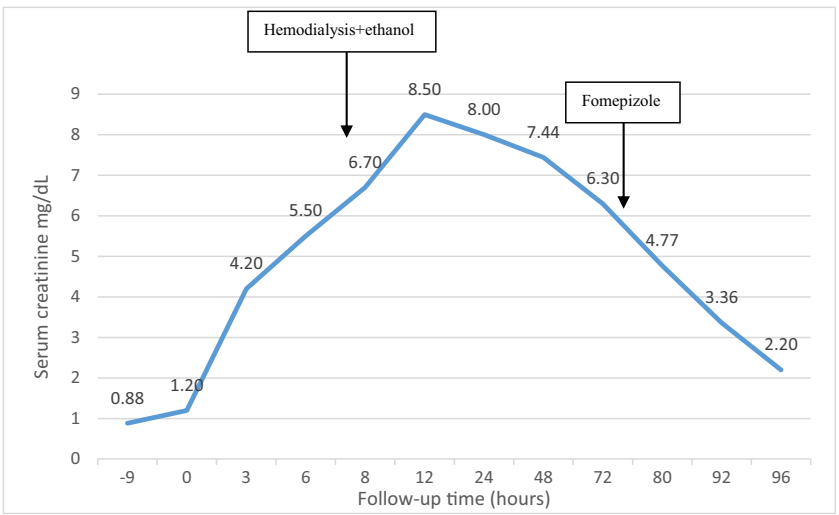


Fig. 1 Serum creatinine monitoring

of fomepizole against ethanol. Numerous pediatric case studies of fomepizole use in EG poisoning have been reported in the literature [6–10]. Therapeutic success and adverse effects are comparable to adult cases. Hemodialysis treatment should be started even when using fomepizole if serum creatinine is high, that is, if there is acute kidney damage. If fomepizole is not available, hemodialysis is recommended at EG serum levels above 500 mg/L, as successful results have been obtained with fomepizole treatment alone in cases without acute kidney damage [1]. Since serum creatinine increased rapidly in our patient, hemodialysis was performed with ethanol treatment. Hemodialysis and ethanol treatment were continued at the initial serum EG level > 200 mg/L, and fomepizole was not immediately available. Our patient's serum creatinine decreased to 2.2 mg/dL, and urine output was 1.5 cc/kg/h 16 h after starting fomepizole.

Conclusion

While EG intoxication is rare in the pediatric population, it should be suspected in a patient with acute kidney injury, metabolic acidosis with increased anion gap, and oxaluria. The diagnosis can be confirmed by serum EG concentration. Early diagnosis and treatment of EG poisoning are important to prevent morbidity and mortality.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Barceloux DG, Krenzelok EP, Olson K, Watson W (1999) American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol 37:537–560
2. Linden CH, Lovejoy FH (1998) Poisoning and drug overdosage. In: Fauci A, Braunwald E, Isselbacher K, Wilson J, Martin J (eds) Harrison's Principles of Internal Medicine, 14th edn. The McGraw-Hill Companies, New York, pp 2534–2535
3. Peces R, Gonzalez E, Peces C, Selgas R (2008) Treatments of severe alcohol poisoning. Nefrologia 28:369–372
4. Scalley RD, Ferguson DR, Piccaro JC, Smart ML, Archie TE (2002) Treatment of ethylene glycol poisoning. Am Fam Physician 66:807–812
5. Hall TL (2002) Fomepizole in the treatment of ethylene glycol poisoning. CJEM 4:199–204. https://doi.org/10.1017/s1481803500006382
6. Caravati EM, Heileson HL, Jones M (2004) Treatment of severe pediatric ethylene glycol intoxication without hemodialysis. J Toxicol Clin Toxicol 42:255–259
7. Baum CR, Langman CB, Oker EE, Goldstein CA, Aviles SR, Makar JK (2000) Fomepizole treatment of ethylene glycol poisoning in an infant. Pediatrics 106:1489–1491
8. Harry P, Jobard E, Briand M, Caubet A, Turcant A (1998) Ethylene glycol poisoning in a child treated with 4-methylpyrazole. Pediatrics 102:e31
9. Benitez JG, Swanson-Biearman B, Krenzelok EP (2000) Nystagmus secondary to fomepizole administration in a pediatric patient. Clin Toxicol 38:795–798
10. Detaille T, Wallemacq P, Clément de Cléty S, Vanbinst R, Dembour G, Hantson P (2004) Fomepizole alone for severe infant ethylene glycol poisoning. Pediatr Crit Care Med 5:490–491

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