

MANAGEMENT OF AN UNRESPONSIVE PATIENT WITH SEVERE ACIDOSIS

Nnaemeka Anyadike, MD, Christie Crawford, MD

Case Report

Congestive heart failure (CHF) is a chronic medical condition whose incidence is rising. The prevalence of CHF is approximately 1% to 3% in Western countries.¹ Despite innovations in medical therapy, CHF is associated with high morbidity and mortality rates.²

CHF patients commonly experience muscle weakness and fatigue as two major symptoms. An altered intracellular handling of ionized calcium has been suggested to play a vital role in impaired myocardial contraction.³ In isolated myocytes from patients with end stage heart failure, systolic ionized calcium levels were markedly decreased, while diastolic levels were elevated as compared to healthy controls.⁴ In addition, digitalis and beta-blocker medical therapy is frequently used in CHF patients and is known to increase myocardial ionized calcium levels.⁵

The patient's past medical history was notable for fibromyalgia and migraine headaches, and her past surgical history included a tonsillectomy. Her past psychiatric history was significant for depression and a prior suicide attempt, involving wrist slitting. The patient had no known drug allergies and her medications included valium, topamax, oxycontin, percocet and lunesta as needed. She did not take any over the counter medications or herbal supplements. The patient consumed alcohol occasionally and smoked cigarettes, but did not use any illicit drugs. Her family history was unremarkable.

Upon admission, the patient's vital signs were notable for a temperature of 102°F and a heart rate of 140 beats per minute. Physical exam revealed dry mucous membranes and tachycardia. On neurologic exam, the patient was found to be unresponsive to all stimuli, including sternal rub. Neurologic exam was remarkable for a left pupil that was sluggishly reactive to light, a right pupil that was midposition and fixed, and the absence of a gag reflex and corneal reflexes. Routine laboratories were notable for a white blood cell count of 31B/L, hemoglobin 17.6g/dL, serum sodium 150mmol/L, serum chloride 118mmol/L, bicarbonate 5mmol/L, creatinine 1.6mg/dL, and an anion gap of 31mmol/dL. Also of note, an arterial blood gas performed at the time of presentation showed a pH of 6.76, PCO₂ 32mmHg, PO₂ 345mmHg, bicarbonate 4mmol/L, and an oxygen saturation of 99% on 100% FIO₂. A CAT scan of the head at the time of admission showed diffuse cerebral edema with no infarct identified.

Hospital Course

This critically ill patient with a severe metabolic acidosis was admitted to the intensive care unit. She was aggressively hydrated and started on a bicarbonate infusion for treatment of her acidosis. She was also given a dose of mannitol to reduce the risk of cerebral herniation in light of her diffuse cerebral edema. Additionally, she was started empirically on broad spectrum antibiotics. As there was a concern for a possible suicide attempt via an overdose, a

urine drug screen, an acetaminophen level, a salicylate level, a serum ethanol level, and serum and urine osmolalities were obtained. These laboratories were remarkable for benzodiazepines in the patient's urine and a serum osmolality of 394mOsmol/kg, resulting in an osmolar gap of 89.1mOsmol/kg.

At this point, the differential diagnosis included ethylene glycol, isopropyl alcohol, or methanol toxicity and laboratories for these toxins were sent. Poison control was contacted and the patient was started on fomepizole infusion at 15mg/kg. The patient's clinical condition continued to deteriorate. Her acidosis and acute renal failure worsened, necessitating the initiation of continuous venovenous hemodialysis. The patient remained unresponsive, and neurology consultation deemed that her prognosis was extremely poor.

On the second day of hospitalization, the patient's metabolic disturbances continued to worsen, and she developed lactic acidosis with rhabdomyolysis. Her ethylene glycol level came back elevated at 39mg/dL. Since all other avenues of treatment had been exhausted and patient's clinical status was continuing to decline, Thomas Jefferson University Hospital's hypothermia protocol was initiated.

After 24 hours, patient was rewarmed and her electrolyte disturbances and acidosis began to resolve. The patient, however, remained unresponsive. On the fourth day of hospitalization, the patient's neurologic status began to improve, as she was able to open her eyes and move her extremities. At this point, she was noted to have right sided weakness so a CAT scan of her head was repeated, which showed a new left occipital lobe infarction and slightly decreased cerebral edema.

On the sixth day of hospitalization, the patient began following commands and was extubated. At this point, her mental status was completely back to baseline and she had no neurologic deficits. Her renal function remained poor and she was continued on hemodialysis. The patient was transferred to inpatient psychiatry on day 10 of her hospitalization. While on the inpatient psychiatry floor, her renal function improved and dialysis was discontinued. She was discharged home from inpatient psychiatry after 12 days, with no residual neurological symptoms.

Discussion

Although not a significant cause of mortality in the US, ethylene glycol consumption is responsible for dozens of fatal intoxications annually. It is a major constituent of antifreeze, de-icing solutions, windshield wiper fluid, solvents, cleaners, and fuels. Typically consumption is due to suicide attempt but can also be secondary to ethanol substitution or accidental consumption. Significant toxicity can be seen with consumption of small amounts, and toxic levels of 1g/kg are considered lethal.^{1,2}

Ethylene glycol is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase. The parent molecule itself is nontoxic, but is noted to cause CNS depression. Its metabolites, primarily glycolate, glyoxylate and oxalate are responsible for the toxic effects of ethylene glycol. Upon consumption, ethylene glycol is rapidly absorbed by the stomach and small intestine, achieving peak concentrations within one to two hours. The half-life of ethylene glycol ranges from 3 to 9 hours or longer if alcohol dehydrogenase is inhibited.³

Typically, the progression of symptoms from ethylene glycol consumption includes initial CNS symptoms, followed by cardiopulmonary manifestations, and ultimately renal involvement. The presentation can be largely variable depending on the amount ingested, the degree of metabolism, and the presence of ethanol co-ingestion. A wide spectrum of systemic effects can occur. In addition, in the preterminal stage of the illness, cerebral herniation and multi-system organ failure are often present.^{1,2}

Blood work typically reveals a profoundly elevated anion gap metabolic acidosis with a lactate level insufficient to account for the degree of acidosis. Also, the patient can have an elevated plasma osmolar gap. However, no single laboratory study, with the exception of an elevated serum ethylene glycol level, is definitively diagnostic for ethylene glycol poisoning. A serum osmolar gap is present in a variety of intoxications including ethanol, isopropyl alcohol, and methanol toxicity.^{1,3}

A high clinical suspicion for intoxication and early treatment are essential for the successful management of a patient with ethylene glycol ingestion. The core components of managing ethylene glycol toxicity include maintenance of cardiopulmonary function as well as the use of the alcohol dehydrogenase antagonist fomepizole, sodium bicarbonate infusion, hemodialysis, and consultation with medical toxicology and poison control.¹

Generally, the use of intravenous sodium bicarbonate is recommended for metabolic acidosis with a pH less than 7.3. Infusions have been shown to increase excretion of active metabolites, as well as decrease end organ damage. Fomepizole is an antidote for methanol and ethylene glycol poisoning that acts as a competitive antagonist of alcohol dehydrogenase. It has a binding affinity of greater than 8,000 times ethanol and has efficacy that may obviate the need for hemodialysis. Hemodialysis rapidly removes toxic metabolites and is mostly indicated for use in patients with acute renal failure, as renal function may take days to months to recover.⁴ The hypothermia protocol utilized in our patient has no evidence-based support for treatment of ethylene glycol associated cerebral edema. Its established use has been in patients who are status post cardiac arrest to preserve neurological function in the setting of cerebral hypoperfusion. Bernard et al. conducted a study of 77 subjects randomized to normothermic and hypothermic treatment after ventricular fibrillation arrest and resuscitation with a significant

improved survival in the group receiving hypothermic cooling.⁵ Similar findings were noted in the Hypothermia After Cardiac Arrest Study Group as well.⁶ A study using animal models elucidated mechanisms by which hypothermia may be neuroprotective including: decreased excitotoxic neurotransmitters, diminished oxidative stress, suppressed cerebral edema preserving blood brain barrier, decreased post-ischemic inflammation, normalized acid-base status in brain, and restoration of protein synthesis.⁷

At Thomas Jefferson University Hospital, the hypothermia protocol was adopted for use with patients status post cardiac arrest. However, given this patient's neurological presentation, the protocol was instituted for neuroprotective purposes. In addition, intoxication due to ethylene glycol was the cause of her neurological dysfunction and also a contraindication to the use of hypothermic cooling per the institution's protocol. However, in our patient's case there were several mitigating circumstances: the threat of herniation, inability to use mannitol due to her elevated serum osmolality, and her young age that warranted the use of hypothermic cooling.

References

1. White SR, Kosnik J. Toxic Alcohols. Marx: *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 6th edition.
2. Scalley RD et al. Treatment of Ethylene Glycol Poisoning. *American Family Physician*. Sep 2002; 66; 5.
3. Poldeski V et al. Ethylene glycol-mediated tubular injury: identification of critical metabolites and injury pathways. *American Journal of Kidney Diseases*. Aug 2001; 38; 2.
4. Bestic M; Blackford M; Reed M. Fomepizole: A critical Assessment of Current Dosing recommendations *J Clin. Pharmacol*. 2009; 49; 130.
5. Bernard SA, Gray TW, Buist M., et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N England J. Medi* 2002. Feb 21;346(8):557-63.
6. HACA study group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346(8):549-56.
7. Axelrod YK, Diring MN. Temperature Management in Acute Neurologic Disorders. *Neurol Clin* 26 (2008) 585-603.