An Unusual Case of Elevated Anion Gap Metabolic Acidosis

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Introduction

- Acute acetaminophen hepatotoxicity causes anion gap metabolic acidosis secondary to lactic acidosis and renal failure
- However, chronic ingestion of therapeutic doses of acetaminophen can sometimes cause elevated anion gap metabolic acidosis through glutathione depletion and 5-oxoproline accumulation
History

- 63 y/o female smoker who has been feeling increasingly weak over the past 2 weeks presents to the hospital with unresponsiveness.
- Has been taking acetaminophen at therapeutic doses for chronic pain, arthralgia and fibromyalgia.
- Intubated en route to the hospital for agonal breathing.
Past Medical History

- **Chronic calcific pancreatitis** secondary to chronic alcohol abuse
- H/O alcohol abuse, abstinent for more than 2 years
- Pancreatic insufficiency leading to severe malnutrition
- **Type 2 diabetes mellitus**
- Depression
- Polyarthralgia/Fibromyalgia
- Chronic back pain
Physical Exam

- **VITAL SIGNS:** Temperature 96 F, PR: 95, RR: 28, O2 100% on 60% FiO2, BP: 117/73; Weight: 33 kg
- **GENERAL:** Emaciated, not responsive to any stimuli
- **HEENT:** Atraumatic. Pupils equal, round, and nonreactive to light. Mild pallor present
- **LUNGS:** Coarse breath sounds right > left
- **CVS:** S1 and S2, RRR. No murmurs, rubs, or gallops
- **Abdomen:** Soft, nontender, nondistended. Bowel sounds +. No organomegaly.
- **EXTREMITIES:** Slightly cool to touch; 2+ pulses. No pitting pedal edema.
Labs

- **CMP:** T Bil: 0.2, AST: 43, ALT: 15, Alkaline phosphatase: 164, Albumin: 2.6, Ca: 7.8, Na: 134, K: 4.8, Cl: 108, HCO3: 3, Urea: 24, Creat: 1.6, Glucose: 384
- **CBC:** WBC: 51.1, Hemoglobin: 9.4, Platelets: 629
- **Urine drug screen:** Tricyclics + Barbiturates
- **Urinalysis:** Unremarkable
- **Rapid blood screen:** Alcohol: NEG; Salicylates: 2.5 (2.0-29.9); Acetaminophen 13 (0-10)
- **ABG:** pH: 6.81, pCO2: 27, pO2: 389
- **Lactate:** 0.5 (0.0-1.6)
Blood osmolality: 319 (282-305) mOsm/kg
Calculated blood osmolality: 298 mOsm/kg
β-hydroxybutyrate: 4.04 (0.03-0.3)
High sensitivity troponin I: 37
Blood cultures: No growth
Imaging

- **Chest x-ray:** Multifocal air space opacities
- **Head CT scan:** No evidence of mass, intracranial hemorrhage, or large distribution acute infarction
Hospital Course

- Broad spectrum antibiotics
- Bicarbonate infusions followed by continuous drip
- Resuscitation fluids
- Vasopressors
- Regular insulin drip as per DKA protocol
What is Going on Here?
Causes of Anion Gap Metabolic Acidosis

- M – Methanol
- U – Uremia
- D – DKA, drugs (Metformin, Stavudine, Topiramate)
- P – Paraldehyde, phosphate
- I – Iron, Isoniazid, ischemia
- L – Lactic acidosis
- E – Ethylene glycol
- S – Salicylates, starvation
Hospital Course cont...

- IV N-acetylcysteine
- Urine 5-oxoproline levels
- Hemodialysis
Hospital Course cont...

- Urine 5-oxoproline levels – 8800 μmol/mol creatinine (reference range <50)
- Very high peak of urine acetaminophen
Increased Anion Gap Metabolic Acidosis as a Result of 5-Oxoproline (Pyroglutamic Acid)
**γ-Glutamyl Cycle**

- Cysteine → Glutamic Acid
- 5-oxoprolinase* (low capacity)
- γ-glutamyl-cysteine synthetase
- γ-glutamyl cysteine
- 5-oxoproline
- γ-glutamyl cyclotransferase
- Acetaminophen
Acetaminophen and 5-Oxoproline

Contributory factors:

- Severe malnutrition (limited glycine and cysteine availability)
- Pregnancy
- Strict vegetarian diet
- Diabetes mellitus type 2
- Liver disease
- Renal failure

Fenves AZ et al; Clinical Journal of the American Society of Nephrology 2006
Diagnosis

- Urine/blood organic acid levels – 5-Oxoproline
- Glutathione synthetase activity
- Supra-therapeutic/toxic levels of acetaminophen are not required to cause 5-oxoprolinuria
Treatment of 5-Oxoprolinemia

- No convincing evidence for N-acetylcysteine
- Bicarbonate infusions and drips
Take Home Points

- In severely malnourished patients, especially women with multiple underlying co-morbidities, chronic ingestion of therapeutic doses of Acetaminophen can cause unexplained severe anion-gap metabolic acidosis with normal lactate levels and elevated serum osmolality.

- If high suspicion get serum/urine 5-oxoproline levels, withdraw medication and start N-acetylcysteine and bicarbonate drip.
Replace MUDPILES?

- G – Glycols
- O – Oxoproline
- L – L-lactate
- D – D-lactate
- M – Methanol
- A – Aspirin
- R – Renal failure
- K – Ketoacidosis

Mehta et al; Lancet 2008
Questions?