September 2017 Critical Care Case of the Month

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A 73-year-old man presented with a three-day history of diffuse abdominal pain, decreased urine output, nausea and vomiting. His past medical history included diabetes, coronary artery disease, hypertension and chronic back pain. The patient reported being started on hydrochlorothiazide, furosemide, pregabalin and diclofenac within the last week in addition to his long-standing metformin prescription.

Initial vitals were significant for tachypnea, tachycardia to 120 bpm, hypothermia to 35ºC and hypotension with a blood pressure of 70/40 mm Hg. Physical exam was remarkable for bilateral lung wheezing and significant respiratory distress. Laboratory examination was concerning for a pH of 6.85, pCO2 of < 5mmHg, serum lactate of 27mmol/l, WBC of 15.6 $x10^6$ cells/cc and a serum creatinine of 8.36 mg/dl. A chest X-ray showed evidence of mild pulmonary edema and a CT of the abdomen did not show any acute pathology.

What is the most likely etiology of the patient's severe acidosis?

1. Diabetic ketoacidosis
2. Ethylene glycol poisoning
3. Metformin-associated lactic acidosis
4. Septic shock

Correct!
3. Metformin-associated lactic acidosis

The most likely cause of the acidosis in this situation is metformin-induced lactic acidosis (1). The patient was intubated for respiratory failure secondary to severe non-compensated metabolic acidosis and shortly thereafter was started on maximal pressor support with norepinephrine, vasopressin, epinephrine and phenylephrine. Continuous renal-replacement therapy and a sodium acetate drip (chosen due to a hospital and nation-wide bicarbonate shortage) were initiated for the acidosis.

How does sodium acetate improve metabolic acidosis?

1. Converted in the liver to bicarbonate ion
2. Enhanced renal reabsorption of bicarbonate
3. Through enhanced chloride excretion
4. Trapping hydrogen ion

Correct!
1. Converted in the liver to bicarbonate ion

Acetate is converted in the liver to bicarbonate (2). Mean arterial pressures remained in the low 50's despite maximal vasopressor support and acidosis was unchanged. A bolus of methylene blue (2mg/kg) was administered with modest improvement in blood pressure (3).

What is the mechanism of action of methylene blue to improve shock?

1. Direct vasoconstriction of arterioles
2. Increases synaptic release of norepinephrine
3. Inhibition of nitric oxide synthetase, and nitric oxide production
4. Tyrosine kinase inhibition

Correct!
3. Inhibition of nitric oxide synthetase, and nitric oxide production

After approximately 9 hours of continuous renal replacement therapy the patient's acidosis was minimally improved, hypotension persisted, and a subsequent bolus of methylene blue was administered but with no improvement in blood pressure. A small supply of sodium bicarbonate was able to be obtained with regular pushes given to maintain MAPs in the 50's. After 14 hours, the acidosis began to correct and the patient's hypotension began to resolve. Vasopressors were titrated off within 30 hours of admission.

This is a case of metformin associated lactic acidosis (MALA) in the setting of iatrogenically induced acute renal failure due to rapid initiation of multiple potentially nephro-toxic medications. Treatment for MALA is mainly supportive to allow time for metabolism of metformin and correction of metabolic acidosis. With such a profound acidosis CRRT requires significantly more time to affect acid base levels and multiple interventions were required in an effort to allow time for this reversible cause of metabolic acidosis to clear. The patient in question had a return of renal function to baseline, is no longer dialysis dependent, and was discharged home.

References

1. Renda F, Mura P, Finco G, Ferrazin F, Pani L, Landoni G. Metformin-associated lactic acidosis requiring hospitalization. A national 10 year survey and a systematic literature review. Eur Rev Med Pharmacol Sci. 2013 Feb;17 Suppl 1:45-9. [PubMed]
2. Neavyn MJ, Boyer EW, Bird SB, Babu KM. Sodium acetate as a replacement for sodium bicarbonate in medical toxicology: a review. J Med Toxicol. 2013 Sep;9(3):250-4. [CrossRef] [PubMed]
3. Warrick BJ, Tataru AP, Smolinske S. A systematic analysis of methylene blue for drug-induced shock. Clin Toxicol (Phila). 2016 Aug;54(7):547-55. [CrossRef] [PubMed]