Shock and Acidosis – a complicated case
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Case Presentation:
47 year-old male is found unresponsive in his bathroom with empty bottles of carvedilol, metformin, and tequila next to him. He was intubated in the field by EMS. Initial vitals by EMS are: blood pressure of 60/40 mmHg and a heart rate of 63 bpm. He is brought to the ED.

What are you going to do first?
How are you going to manage this patient?
What things should you be thinking about?

The initial management in the ED was with isotonic crystalloid, vasopressors (norepinephrine, dopamine, epinephrine) as well as a bicarbonate infusion and intravenous doses of glucagon. Initial labs revealed a Creatinine of 2.6 units?, ABG had a pH of 7.13, pCO2 of 30 mmHg and a bicarbonate of 10 units?. Due to the suspicion of a toxic bradycardia due to a beta blocker and/or a calcium channel blocker, high dose insulin therapy (dose?) was initiated and the patient was admitted to the ICU. A serum lactate later results, and was 17.5. The patient was persistently hypotensive and acidotic, and was placed on hemodialysis by the nephrology service.

Discussion:
I found this case very interesting. Firstly, this patient took two medications that can be deadly in overdose, and they can both present with similar symptoms. First we will discuss beta blocker overdose, followed by MALA (metformin-associated lactic acidosis).

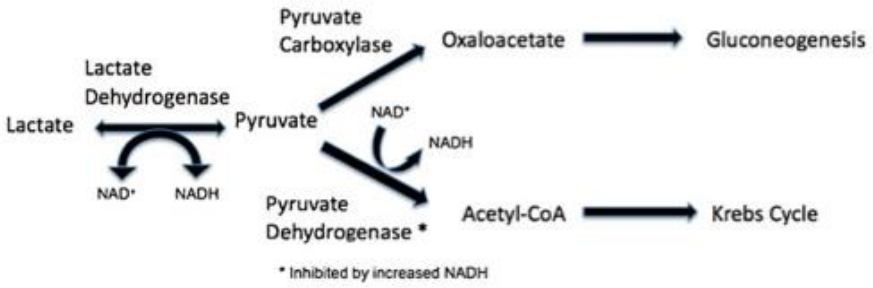
Patients with beta blocker overdose will present with **hypotension, bradycardia, decreased SVR and cardiogenic shock**, as seen in our patient. The treatment for this involves intravenous **atropine, calcium salts, and glucagon**. Atropine is a vagolytic agent that increases heart rate. The calcium salts try to overcome calcium channel blockade by increasing the transmembrane calcium gradient. When using calcium salts, calcium chloride has more calcium per unit, but causes tissue necrosis if it extravasates. It should be used in cases of cardiac arrest and only when a central line is available. Calcium gluconate has less available calcium but is much less irritant. Glucagon, which stimulates increases in cAMP in the cardiac myocyte in a similar mechanism as beta agonists (via G protein coupled receptor), leads to eventual calcium release from the sarcoplasmic reticulum and increased cardiac contractility.

Following these treatments, **high-dose insulin and glucose** is recommended (also called hyperinsulinemia-euglycemia therapy). Both CCBs and BBs result in impaired fatty acid metabolism by the heart, and states of impaired glycogenolysis and lipolysis. CCBs also result in hyperglycemia due to impaired insulin release. Insulin switches the metabolism to one using carbohydrates. This leads to increased cardiac inotropy, increased intracellular glucose transport, and increased cardiac output. Dosing for this is a 1 U/kg bolus of regular insulin, followed by an infusion of 0.5-1 U/kg/hr, to a max of 10 U/kg/hr.

A last resort can be to try and use **Intralipid, or lipid rescue infusion**. This treatment uses 20% intralipid solution, the same one used for TPN, to augment the lipid compartment in the blood.

This acts as a “sink” where lipid soluble medications can dissolve and remain in the blood compartment instead of in the tissues. The dose used is 1.5 ml/kg as a bolus, followed by 0.25 ml/kg/min for 30-60 minutes.

Metformin is a widely used agent for the management of diabetes. MALA (metformin-associated lactic acidosis) can be seen in **acute** ingestions, as was the case in our patient, as well as in patients who are on metformin **chronic**ally. In general, lactic acidosis is defined as a serum pH of less than 7.35 and a serum lactate greater than 5 mmol/L. It is considered a type B acidosis in the Cohen-Woods classification. Metformin works via reducing gluconeogenesis, increasing peripheral uptake of glucose, and decreasing fatty acid oxidation. This in turn **increases lactic acid formation**. Metformin also inhibits pyruvate carboxylase, further increasing accumulation of lactate.



Metformin is excreted unchanged by the **kidneys**. In cases where renal excretion is reduced, or in cases where the amount ingested saturates this excretion process, metformin accumulates.

The incidence of MALA is low, however the **reported mortality is high at 50%**. Signs and symptoms of metformin overdose include **nausea, vomiting, abdominal pain, malaise, myalgias, mental status changes, renal insufficiency, and cardiovascular compromise secondary to severe acidosis**. The exact diagnostic criteria for MALA s not well defined in the literature, however Peters et al describe the following: metformin overdose in the setting of suicide attempt or patient on metformin chronically, lactic acidosis with a lactate of 5 mmol/L or greater, and a bicarbonate of less than 22 mmol/L.

The mainstay of treatment for MALA is supportive. Bicarbonate infusions have been used to treat the severe metabolic acidosis. **Hemodialysis** has also been recommended**, although currently it has not been proven to be beneficial**, which was also shown in the Peters et al paper. The treatment should have two main goals: **restore adequate acid base status and remove metformin from the body**. The characteristics of metformin, highly water soluble, low molecular weight and minimally protein bound, lend to its ability to be dialyzed effectively. Dialysis should be started early, sometimes before severe lactic acidosis occurs, secondary to the drug having a large volume of distribution. This will allow removal of the drug before it redistributes into tissues. Using bicarbonate dialysate may also increase metformin clearance. Activated charcoal should be given in the acute period to limit absorption of the drug. Intralipid has not been shown to be of benefit to this highly water-soluble drug.

The big challenge in these patients is when to start dialysis. There is currently no predictive

model available to guide treatment strategies, and frequently patients will start developing lactic acidosis once the drug has redistributed to the tissues. Recommendations continue to be **early gastric decontamination followed by supportive care with intravenous hydration and consideration of early hemodialysis with bicarbonate dialysate**. This particular case was difficult as some of the symptoms of beta-blocker overdose (hypotension, shock) can also lead to development of lactic acidosis. Ultimately, our patient's clinical picture was likely multifactorial.

Case Conclusion

Our patient required high dose insulin, glucagon, and multiple pressors for 24 hours. The nephrology service was consulted and he was placed on CRRT. His lactate was persistently elevated during the first 24 hours. His profound academia also persisted for about 24 hours (pH of 7.1). Once dialyzed, his pH normalized and his lactate cleared. We were able to wean his pressors and insulin. He was continuously monitored for hypoglycemia. He was extubated 50 hours following admission and subsequently discharged home.

Further Reading

- http://pubmed.org/pubmed/20887905
- http://pubmed.org/pubmed/18571361
- http://pubmed.org/pubmed/24483200