Metformin toxicity

April 11, 2019 by Josh Farkas

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physiology of metformin-induced lactic acidosis

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**primary mechanism of toxicity**

- The main effect of metformin is inhibition of the mitochondrial transport chain complex-I, which essentially poisons the mitochondria.
- The mitochondrial transport chain is generally the final component of metabolism which generates ATP using NADH (above). If the mitochondrial transport chain stops working:
  - NADH builds up
  - The Krebs cycle eventually gets backed up
  - Pyruvate gets converted into lactate (rather than moving into the Krebs cycle)

**epidemiology & definitions**

The following definition system has emerged within the past couple years. It hasn't been uniformly adopted, but it seems to be emerging as the best way to understand metformin toxicity.
High levels of metformin are the primary cause of illness.

(1) Acute metformin overdose
   - Acute poisoning may lead to MILA in the absence of renal dysfunction.
   - Precise amount of metformin required to do this is unclear, but seems to be high (e.g. >20 grams).\(^3\)
   - Patients with acute ingestion look fine initially, but deteriorate subsequently ("toxin bomb").

(2) Subacute accumulation of metformin due to renal failure
   - Metformin is renally cleared.
   - Progressive renal failure (with GFR << 30 ml/min) eventually leads to metformin accumulation and toxicity.
   - These patients may present with marked lactic acidosis, yet have fairly preserved hemodynamics and look OK.

**metformin-associated lactic acidosis (MALA)**

- Definition:
  - Patient on metformin develops an acute life-threatening illness (e.g. septic shock, cardiogenic shock).
  - **Metformin amplifies the degree of lactic acidosis, but it's not the sole cause of the illness.**
- Risk factors include renal insufficiency, higher doses of metformin, and alcoholism.

**metformin-unrelated lactic acidosis (MULA)**

- Metformin levels are low; metformin is an innocent bystander.
- Clinically it will be impossible to differentiate this from MALA
  - Differentiation of MULA from MALA requires measurement of metformin levels, which isn't available at most hospitals.

**clinical presentation**

**signs & symptoms of metformin toxicity**

- Vitals: The following abnormalities may be seen:
  - Hypothermia
  - Hypotension progressing to vasopressor-refractory shock can occur.
- **GI symptoms** often predominate: Nausea, vomiting, diarrhea, epigastric pain.
- **Delirium**, decreased consciousness

**evaluation**

- Fingerstick glucose (hypoglycemia may occur)
- ABG or VBG
- Complete set of chemistries (including Ca/Mg/Phos), Coags
- **Anion-gap labs**:
  - Lactate level (requisite for diagnosis)
  - beta-hydroxybutyrate level (frequently elevated)
- Liver function tests
- If infection is possible: Blood cultures, urinalysis, chest X-ray, procalcitonin.

https://emcrit.org/ibcc/metformin/
Note that many patients may be ill due to a combination of metformin plus an acute illness. Therefore, a thorough search must always be made for any additional causes of physiologic stress.

**metformin-induced lactic acidosis vs. DKA**
- Compared to isolated DKA, patients with metformin-induced lactic acidosis have greater degree of hyperlactatemia, with less extensive ketoacidosis.
- It can be very difficult to sort this out in some situations. When in doubt, treat both conditions (the treatment for DKA may actually improve MILA/MALA). More on treatment of this below.

**other causes of lactic acidosis, for example:**
- Shock of any etiology (septic shock, adrenal insufficiency, cardiogenic shock, etc.)
- Acute mesenteric ischemia
- Seizure
- Liver failure
- Thiamine deficiency
- Medications
  - HIV antiretrovirals
  - Linezolid
  - Propylene glycol
  - Propofol infusion syndrome
  - Beta-adrenergic medications (e.g. albuterol, epinephrine)
  - Massive acetaminophen overdose

**prognosis**

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**acute metformin intoxication**

[https://emcrit.org/ibcc/metformin/](https://emcrit.org/ibcc/metformin/)
Poor prognostic signs:
- More severe acidemia (pH < 6.9)
- Higher lactate levels (>15 mM)
- Prolongation of prothrombin time (INR)

**chronic metformin use**

- Lactate level and pH seem to lack prognostic significance in these patients. The reason for this is that historically patient cohorts have contained a mixture of MILA, MALA, and MULA. With such a heterogeneous group of patients, prognostic relationships get muddied.

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**decontamination after acute ingestion**

- Activated charcoal may be considered for patients who present very shortly following acute ingestion, without contraindications (e.g. normal mental status without risk of aspiration).

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**exclusion of other illness & empiric therapy for sepsis**

- Evaluate for alternative causes of illness, especially septic shock.
- If sepsis is possible, consider empiric antibiotic therapy (along with further diagnostics, including blood cultures and possibly procalcitonin levels).
  - Antibiotics may be discontinued within 24-48 hours if additional evidence of sepsis doesn't emerge over time.

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**glucose administration & diabetes management**

1) basic glucose management (all patients)

- Follow fingerstick glucose frequently.
- Provide IV dextrose as needed.

2) treatment of diabetic ketoacidosis?

- Diabetic ketoacidosis may be tricky to diagnose in the context of metformin:
  - Metformin itself may promote the catabolism of fats and production of ketoacid.
  - Metformin may cause hypoglycemia (so the patient may not have features of classic diabetic ketoacidosis).
  - In some cases, it may be hard to sort out whether the patient has euglycemic DKA versus metformin poisoning (and to some extent this may be a linguistic issue).
  - A case series of three patients with metformin-associated lactic acidosis and concurrent euglycemic DKA reported clinical improvement when treated with glucose infusion and dialysis alone (without an insulin infusion). This suggests that the presence of ketoacidosis alone doesn't mandate insulin therapy. However, persistent euglycemic DKA which doesn't improve may be an indication for insulin therapy (more on euglycemic DKA [here](https://emcrit.org/ibcc/dka/#euglycemic_DKA)).

3) glucose, insulin, and potassium (GIK therapy) ???
Insulin therapy may be beneficial for metformin poisoning (aside from any question of DKA). Benefits of insulin may include the following:\(^5\)

- Reduced generation of lactate because of:
  - Reduced catabolism of protein into pyruvate
  - Reduced NADH/NAD ratio
  - Stimulation of pyruvate dehydrogenase activity (PDH), which tends to push pyruvate into the Krebs cycle
  - Reduced catabolism of fat will tend to decrease ketoacid production (thereby improving pH)
- If given to patients with normal glucose and potassium levels, then insulin must be *accompanied* by the administration of glucose and potassium (hence the name “GIK therapy”).
- There is only very weak evidence to support this therapy:
  - Seems to reduce lactate levels in dogs poisoned by phenformin.\(^6\)
  - Retrospective case series of phenformin poisoning suggest that insulin was helpful.\(^5\)
- GIK therapy *cannot* be recommended for routine therapy. However, if nothing else is working and the patient is actively dying, this might be worth a try?
  - (Of course, talk to your toxicologist if possible before doing this)

**volume resuscitation**

Assess volume status in the usual fashion and replete as necessary to target euvoolemia. Patients won’t necessarily be hypovolemic, but they may often be.

**bicarbonate?**

- Undesirable for a few reasons:
  - Might increase cellular permeability to metformin.
  - Bicarbonate has never been shown to be a useful therapy for *lactic acidosis*.
  - Raising the pH with bicarbonate may actually stimulate glycolysis and thereby *increase* lactate generation.\(^7\)
- Often quoted as being a component of “standard therapy.” However, bicarbonate is supported by no evidence here and seems undesirable (unless the bicarbonate level is extremely low, for example <5 mEq/L).\(^5\)

**other options aren’t great either**

- Normal saline is an acidic fluid that will exacerbate the acidosis.
- Lactated Ringers isn’t a good choice, as these patients cannot metabolize lactate.
- Plasmalyte or normosol aren’t good either (they contain acetate which is normally metabolized into bicarbonate via the Krebs cycle – but may not be metabolized properly in this situation).
compromise options?

- No matter what you do here, folks will find fault with it. The following are two compromise options which might represent a reasonable middle-ground:
  - (1) D5W with 1/2 normal saline, plus one ampule (50 mEq) of bicarbonate added per liter.
  - (2) Simultaneous infusions of normal saline and isotonic bicarbonate
    - If the saline is infused about six times faster than the bicarbonate, the combination will produce an isotonic fluid with an effective bicarbonate concentration of 25 mEq/L (Strong Ion Difference of 25 mEq/L).
    - This allows you to resuscitate mostly with normal saline, but at the same time not exacerbate the acidosis.

respiratory support

- Intubation usually isn’t necessary (if it is, increase minute ventilation to compensate for acidosis).
- High-flow nasal cannula may be used to improve ventilatory efficiency and reduce the work of breathing, for a patient with substantial acidosis and Kussmaul respiration, who is at risk of tiring out.
  - In this application, the flow rate should be increased as high as tolerated, with a low FiO2 (e.g. 50-60 liters/minute flow with 30% FiO2).

dialysis

EXTRIP indications for dialysis

- Main indications
  - Lactate >15-20 mM
  - pH <7.0-7.1
  - Failure to improve despite standard supportive measures
- Comorbid conditions which may lower the threshold for dialysis
  - Shock
- Impaired kidney function
- Liver failure
- Decreased level of consciousness

Who benefits most from dialysis?

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<thead>
<tr>
<th>MILA</th>
<th>MALA</th>
<th>MULA</th>
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<td>metformin induced lactic acidosis</td>
<td>metformin associated lactic acidosis</td>
<td>metformin unrelated lactic acidosis</td>
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additional thoughts regarding dialysis

- In addition to the above criteria, the overall clinical context and diagnosis needs to be considered. For example, in a patient with a pH of 6.95 due mostly to a non-anion gap metabolic acidosis (with a lactate level of 3 mM), dialysis might not be needed.
- The benefit of dialysis is probably greatest in MILA patients, with extremely elevated metformin levels.

if dialysis is performed:

- It should ideally be continued until the lactate <3 mM and pH >7.35.
- Hemodialysis is preferable to continuous renal replacement therapy (to achieve adequate clearance of metformin).

methylene blue??

potential mechanism of action

- (1) Metabolic rescue
  - The main problem in metformin-associated lactic acidosis is blockade of electron transport at Complex I on the mitochondria.
  - Methylene blue is capable of accepting electrons from NADH and transferring them to cytochrome c in the mitochondria (bypassing Complex I). This should function as a bridge to re-establish the flow of electrons through the mitochondria. Theoretically this could be a silver bullet which re-starts the stalled Krebs cycle and re-establishes normal metabolism.
  - However, some evidence suggests that this may not work due to poor cellular penetration by methylene blue.
- (2) Vasoconstriction: Methylene blue can also function as a vasoconstrictor (by scavenging nitric oxide). It's possible that its efficacy in some cases of refractory shock with metformin toxicity is due purely to its efficacy as a vasoconstrictor.

evidence & recommendations?

- Limited to case studies.
- G6PD deficiency is a contraindication, as methylene blue may increase the risk of hemolytic anemia.
- May be considered in cases refractory to conventional therapy.
- A reasonable dose might be 2 mg/kg loading dose over 15-30 minutes, followed by ~0.25 mg/kg/hour infusion.
Metformin associated lactic acidosis

- **Evaluation**
  - Basic labs including glucose, electrolytes
  - Lactate & beta-hydroxybutyrate levels, liver function tests
  - ABG or VRG
  - Acute ingestion: Additional toxicology labs (e.g., acetaminophen & salicylate levels)
  - Possible sepsis: Infectious workup (e.g., blood cultures, urinalysis, CMR, procalcitonin)

- **Glucose management**
  - Follow glucose & administer IV dextrose PRN
  - Persistently & markedly elevated beta-hydroxybutyrate: consider tx for euglycemic DKA?

- **Volume resuscitation**
  - Evaluate volume status and resuscitate if needed to target euvolesma
  - Ideal resuscitative fluid debatable (possibly some combination of a lot of normal saline & some isotonic bicarbonate)

- **Respiratory support**
  - Consider HFNC at high flow rate to reduce work of breathing in marked acidosis

- **Hemodialysis**
  - Indications:
    - Lactate > 15-20 mM
    - pH < 7.0-7.1
    - Failure of standard supportive therapy
  - Lower threshold for dialysis in patients with renal failure, shock, delirium, or hepatic failure

- **Salvage therapy: refractory to avoid measures**
  - Methylene blue
  - GIK therapy (Glucose infusion, Insulin infusion, and potassium)


The Podcast Episode

Want to Download the Episode? [Right Click Here and Choose Save-As](http://traffic.libsyn.com/ibccpodcast/IBCC_EP_32_-_Metformin_Toxicity_Final.mp3)

questions & discussion

To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/metformin/).

- Under-diagnosis: Failure to consider metformin as a cause of lactic acidosis.
- Over-diagnosis: The assumption that all patients with metformin and lactic acidosis have MILA (without any other problems going on). This assumption could lead to overlooking simultaneous problems, such as septic shock plus MALA.
- Trying to fix metformin-induced lactic acidosis with large-volume fluid resuscitation. Unless the patient is hypovolemic, fluid isn't the answer.
• Failing to initiate dialysis in a patient who is extremely ill and meets guideline criteria for dialysis. It's hard to know precisely which patients will benefit from dialysis, but there are probably some who need dialysis to recover. When in doubt, consult your toxicologist and consider a trial of dialysis.

**Going further:**

- [Metformin-associated lactic acidosis](https://litfl.com/metformin-associated-lactic-acidosis/) (Chris Nickson, LITFL)
- [Metformin-associated lactic acidosis](https://coreem.net/podcast/episode-124-0/) (CoreEM, Anand Swaminathan)

**References**


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.