

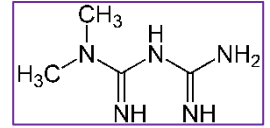


Clinical Pharmacology & Toxicology Pearl of the Week

~ Metformin associated lactic acidosis (MALA) ~

Metformin

- ✓ Metformin is classified as a biguanide oral glucose-lowering drug
- ✓ It is the only biguanide medication currently in use in North America.
- ✓ Metformin reduces hepatic gluconeogenesis, leading to decreased hepatic glucose output
- ✓ It sensitizes peripheral tissues and increases peripheral glucose uptake
- ✓ Metformin also decreases fatty acid oxidation & increases glucose uptake in the intestinal wall



Epidemiology of MALA

- ✓ Incidence of MALA is 1 to 10 per 100,000 patients on metformin
- ✓ Risk factors for the development of MALA include:
 - renal failure
 - liver failure
 - congestive heart failure
 - sepsis
 - hypoxemia

Pathophysiology of MALA

- ✓ Metformin interferes with the activity of the Cori cycle, an enzymatic cycle found in the liver that recycles peripheral lactate and converts it into pyruvate & glucose for use in cellular metabolism
- ✓ At concentrations > 5 µg/mL, metformin binds to complexes of the mitochondrial electron transport chain and inhibits hepatocellular aerobic ATP production → increased lactate production via anaerobic metabolism

Diagnosis of MALA

- ✓ Abdominal pain, gastrointestinal distress and acute kidney injury are common at presentation
- ✓ Clinical presentation also includes symptoms of metabolic acidosis including:
 - Kussmaul respiration
 - altered mental status
 - hemodynamic instability
- ✓ Serum lactate levels correlate positively with serum metformin concentrations in MALA
- ✓ Serum lactate level is a significant predictor of mortality, particularly when lactate level is > 20mmol/L
- ✓ After acute overdose, serum lactate will rise within 6-8 hours post ingestion. Therefore, checking a blood gas on arrival and then again 6-8 hours post ingestion is helpful to follow trends in both acid base status and lactate

Management of MALA


- ✓ Correction of lactic acidosis with bicarbonate infusion may be used
- ✓ Renal replacement therapy may be required, particularly in the setting of refractory severe acidosis and elevated serum lactate levels (especially those greater than 20mmol/L)


Prognosis of MALA

- ✓ The cumulative mortality related to MALA is 16%
- ✓ An initial pH < 6.9 or a serum lactate concentration > 25mmol/L is associated with >80% mortality.

References:

1. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia*. 2017;60(9):1577-1585.
2. DeFronzo R, Fleming GA, Chen K & Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metabolism*. 2016;65(20):20-29

 The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click [HERE](#) for clinical issues the CP service can assist with.

 The Poison and Drug Information Service ([PADIS](#)) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.