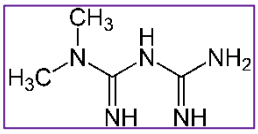
Clinical Pharmacology & Toxicology Pearl of the Week

~ 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 greater than 20mmol/L
- ✓ After acute overdose, serum lactate will rise within 6-8 hours post ingestion, although it may take up to 12 hours. Therefore, checking a blood gas on arrival and then again checking serial gases up to 12 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 20 mmol/L). See the Extracorporeal Treatments in Poisoning (EXTRIP) guidelines for metformin toxicity for more details

Prognosis of MALA

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

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

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