

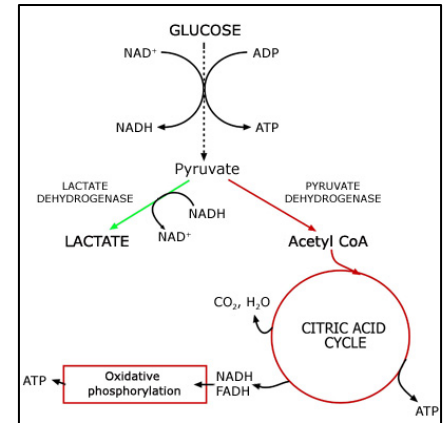


# Clinical Pharmacology & Toxicology Pearl of the Week

## ~ Drug-induced hyperlactatemia ~

### Lactate Production & Metabolism

- ✓ Lactate is formed when pyruvate is reduced via  $\text{NADH} \rightarrow \text{NAD}^+$ , which is facilitated by the enzyme Lactate Dehydrogenase (LDH).
- ✓ Lactate elevation can be classified as either [Type-A](#) or [Type-B](#):
  - Type-A lactate production results from tissue hypoxia.
  - Type-B lactate production occurs despite normal tissue oxygenation in the setting of genetic/metabolic diseases, malignancy & drug-induced causes.
- ✓ Normally, lactate is taken up by the liver where it undergoes enzymatic transformation  $\rightarrow$  pyruvate  $\rightarrow$  glucose as part of the Cori Cycle.



### Drug-induced lactate production

- ✓ Drug-induced hyperlactatemia is typically a type-B hyperlactatemia resulting in tissue hypoxia *independent of* tissue oxygen availability.
- ✓ Hyperlactatemia results from medication induced imbalance between lactate production and metabolism.

**Table 1: Causes of drug-induced hyperlactatemia**

| Cause of lactate elevation                    | Proposed mechanism  | Culprit Medications   |
|---|---|---|
| Increased pyruvate production                 | Cells shunt pyruvate $\rightarrow$ lactate to regenerate $\text{NAD}^+$                             | Beta-2 agonists   |
| Metabolism of drug into lactate               | Direct hepatic metabolism of parent drug to racemic mixture of D-lactate & L-lactate                | Propylene glycol  |
| Interference with Cori cycle                  | Inhibition of Cori cycle leads to reduced oxidation of lactate to pyruvate in liver                 | Biguanides (metformin)                                      |
| Inhibition of mitochondrial protein synthesis | Increased drug-ribosome binding and reduced activity of the electron transport chain                | Oxazolidinone antibiotics (linezolid)                       |
| Inhibition of electron transport chain        | Direct inhibition of electron transport chain leading to decreased $\text{ATP}$ synthesis           | Propofol, sodium nitroprusside, barbiturates, valproic acid |
| Uncoupling of oxidative phosphorylation       | Inhibition of $\text{ATP}$ synthesis via uncoupling of the electron transport chain in mitochondria | Salicylates   |

### Management

- ✓ Rule out causes of a potential Type-A lactic acidosis before considering Type-B causes.
- ✓ Identify & discontinue the offending drug in the event of a suspected drug-induced hyperlactatemia.
- ✓ Supportive care, including hydration where indicated & monitoring for resolution vs. progression.
- ✓ Renal replacement therapy is indicated in cases of severe refractory lactic acidosis such as in the setting of metformin overdose.

### References:

1. Blohm E, Lai J, Neavyn M. Drug-induced hyperlactatemia. *Clinical Toxicology*. 2017; 55(8):869-878. DOI: 10.1080/15563650.2017.1317348



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.