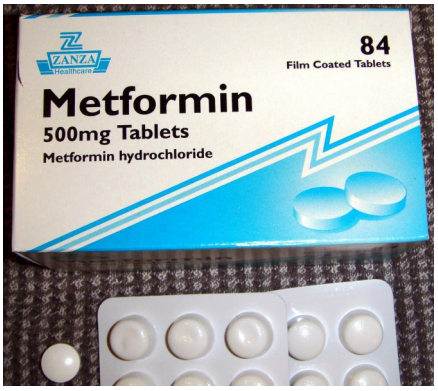
ToxTidbits

Maryland Poison Center
UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY

July 2019 Poison Center Hotline: 1-800-222-1222

The Maryland Poison Center's Monthly Update: News, Advances, Information

Metformin-Associated Lactic Acidosis



Metformin is a critical medication for treatment of type II diabetes mellitus. It is listed in the World Health Organization's list of essential drugs and is one of the few medications for diabetes with improvements in cardiovascular outcomes. Common adverse effects are gastrointestinal in nature but the drug is well tolerated with appropriate dose titration. The fatality rate of single-substance metformin exposures reported to poison centers is 0.5%, which is double the rate of death due to acetaminophen taken alone. The question is why.

The primary mechanism of action of metformin (a biguanide) is decreasing hepatic gluconeogenesis. Secondary effects include increased peripheral glucose utilization, reduced fatty acid oxidation, and enhanced glucose recycling (*Drugs* 1999*;58 Suppl 1:31–9 & 75–82)*. Metformin was not the first biguanide. The first biguanide on the market, phenformin, had limited penetration into the U.S. market due to cases of profound lactic acidosis. In 1961, Daughaday and colleagues published a case series of three patients with lactic acidosis *(N Engl J Med 1962;267:1010-1014).* Later, Bernier published a series of two patients treated with phenformin that developed lactic acidosis. Some of these cases had serum lactate concentrations > 20 mmol/L *(JAMA 1963;184:43-46).* After multiple cases were published, the drug was removed from the U.S. market in 1977.

Metformin is much safer drug than phenformin; the incidence of metformin-associated lactic acidosis is estimated to be 3-6 cases per 100,000 patient-years with chronic use *(Metabolism 2016;65:20-29)*. After overdose, the incidence of hyperlactatemia was 9.1% in one study *(Am J Emerg Med 2010;28:857-861)*. The most common risk factors include older age and decreased kidney function. In general, hyperlactatemia is either due to increased production or decreased clearance. Lactate is primarily cleared by the liver at a rate that usually exceeds production. Metformin may contribute to hyperlactatemia by inhibiting the electron transport chain, inducing anaerobic metabolism. This results in increased lactate production *(Metabolism 2016;65:20-29)*. Furthermore, some authors suggest that metformin also inhibits pyruvate decarboxylase that is necessary for converting pyruvate to oxaloacetate and subsequent gluconeogenesis *(F1000Res December 2015:1-13).* Pyruvate is then available to convert to lactate.

Most cases of metformin toxicity are with chronic use; however, after a large acute overdose, patients can develop symptoms of metabolic acidosis within 4 hours. These include hypertension, tachycardia, diaphoresis, tachypnea, and confusion. Laboratory findings include an elevated lactate and metabolic acidosis. Since metformin inhibits the electron transport chain, many patients progress to profound hypotension requiring vasopressor support.

Management is supportive plus hemodialysis (HD). Data are conflicting regarding the removal of metformin by either intermittent HD or continuous renal replacement therapy (CRRT). Treatment with HD is preferred unless patients are unable to tolerate it, in which case CRRT is often necessary to correct acidemia.

Did you know?

Metformin is one of the most frequently used medications in the United States.

Since 2006, it has been in the top 5 agents dispensed. There are between 54 million and 81 million prescriptions per year. Despite the large number of prescriptions, calls to poison centers about metformin are infrequent, with approximately 9,400 cases or 0.44% of all human exposures reported to US poison centers in 2017.

Jimmy Leonard, PharmD
Clinical Toxicologist

@MPCToxTidbits