

Hypoglycemia with Severe Lactic Acidosis

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A fifty-seven-year-old South African female, of Indian descent, with end-stage renal failure and on regular hemodialysis, was admitted in June 2016. She presented with one-day history of back pain, mild abdominal pain, nausea and vomiting. Initial investigations showed blood glucose less than 1 mmol with lactic acid 13.27 mmol/L.

She was not a diabetic, but her husband was a diabetic on metformin. Despite extensive investigation, the cause of hypoglycemia and life-threatening lactic acidosis was not immediately identified. She received Glucagon and intravenous dextrose and had no hypoglycemia during admission. She was discharged after four days in good condition. Metformin level was sent to an outside laboratory, and revealed a highly elevated level. She admitted that she might have confused her husband's metformin with paracetamol, which tablets look similar.

Bahrain Med Bull 2020; 42 (3): 228 - 230

Metformin is used for the treatment of diabetes mellitus type 2. It is often given alone or in association with other injected and/or oral medications of diabetes. It belongs to the biguanide class of medicines, and inhibits hepatic gluconeogenesis; it increases insulin sensitivity, enhances peripheral utilization of glucose, and decreases uptake of glucose in the alimentary tract¹.

It is essentially utilized to treat diabetes, but it may also be used to treat other certain medical issues that are related to insulin resistance, such as polycystic ovary syndrome.

Metformin-associated lactic acidosis (MALA) is rare; however, it might be a fatal complication.

Lactic acidosis is commonly reported as the most life-threatening adverse event after accidental and intentional Metformin ingestion²⁻⁴. Metformin-induced hypoglycemia however, in the absence of co-ingestion of other antidiabetics, is rare⁵. One review reported hypoglycemia risk to be between 0-21%⁶.

The aim of this presentation is to report a case of hypoglycemia with severe lactic acidosis following accidental ingestion of metformin tablets.

THE CASE

A fifty-seven-year-old South African female of Indian descent, a known case of end-stage renal disease (of unknown etiology, autoimmune screening tests were negative, never biopsied) on hemodialysis presented with nausea and vomiting, back pain, and mild abdominal pain. The abdominal pain was mild and resolved within a few hours. She had approximately ten to

twenty episodes of vomiting, and the vomitus contained only food content and gastric secretion with no blood or bile. There was no history of fever, cough or chest pain, and no change in her bowel or urinary habits. The family denied the ingestion of any drug out of the usual medications.

The blood glucose was less than one mmol, pH 6.8, HCO₃ 3.9, Anion gap 43, Lactate 13.27 mmol/L, Potassium 5.1, and ketones was 7 mg. The patient was commenced on intravenous dextrose and received a stat dose of Glucagon. The initial impression was hypoglycemia with lactic acidosis of unknown cause.

She was managed with Dextrose infusion, a stat dose of Glucagon, and 200 ml of NaHCO₃. Her biochemistry was slow to respond, requiring multiple dialysis sessions before her lactate reduced. During her stay in the hospital, she maintained good urine output. She required IV dextrose for 24 hours to maintain blood sugar level. No attack of hypoglycemia in the hospital, blood sugar readings were between 4.4-7.7 mmol.

Three days later, she was kept fasting for 72 hours to induce hypoglycemia. Her blood sugar levels were stable with no hypoglycemia in the hospital. After four days she was discharged.

However, we did have a high index of suspicion for metformin ingestion as her husband is diabetic and takes metformin. Metformin blood level was sent for testing and extremely high levels were identified in her blood of more than 12.5mg/L (0.5–4 mg/L) on the day of presentation.

On further discussion with the patient, she admitted that she may have confused her husband's metformin with paracetamol.

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DISCUSSION

Metformin, a dimethyl biguanide, is an oral antihyperglycemic agent. It is used as an initial treatment for diabetes mellitus type 2 (T2DM). It is among the most frequently prescribed medicines worldwide⁷. It was approved in the United States by the FDA in 1995⁸.

Metformin ingestion does not produce hyperinsulinemia or hypoglycemia, which are the common adverse effects of other anti-diabetic medications⁷. The mechanisms through which metformin may cause hypoglycemia include reduced production of glucose by the liver and decreased absorption of glucose through the gut⁷.

One of the most common causes of metabolic acidosis among patients who are hospitalized is lactic acidosis. It is recognized as a complication of metformin use, especially in patients with comorbidities, such as renal failure and liver dysfunction.

Lactic acidosis due to metformin use occurs very rarely with an approximate incidence ranging between 0.03 and 0.06 per 1,000 patients per year. As the rate of occurrence of MALA is very low, its exact incidence is unknown¹.

MALA is rare, but potentially fatal. Lactic acidosis is rare; however, it is a serious condition, with a mortality rate of up to 50%⁸. It may be difficult to diagnose lactic acidosis when there is limited history available.

The process of occurrence of MALA is complex. Metformin encourages the transformation of glucose to lactate in the small intestine's splanchnic bed. In addition, Metformin also obstructs the respiratory chain complex 1 in the mitochondria resulting in reduced hepatogluconeogenesis from alanine, pyruvate and lactate. This leads to elevated lactate levels.

MALA may occur in patients with renal insufficiency, hemodynamic instability, liver disease, or other illnesses when a high level of metformin accumulates. Our patient had multiple risk factors, including renal failure. Presumably, there was an accumulation of metformin due to decreased renal clearance.

Typical symptoms of MALA include nausea, abdominal pain, vomiting, myalgia, malaise, and dizziness. One of the early signs is tachypnea, which occurs as a physiological reaction to metabolic acidosis. Symptoms of the gastrointestinal tract are among the common adverse effects when metformin is used therapeutically, in such cases lactic acidosis is not present. More severe or serious cases may present with coma, hypothermia, respiratory insufficiency and hypotension.

The classical triad of MALA is severe lactic acidosis, renal failure, and elevated concentration of metformin. However, the concentration of metformin is often not a readily available laboratory test in most hospitals⁹.

An overdose of metformin may also occur without the presence of renal failure, especially acute overdose.

Severe lactic acidosis is surely not a specific condition related to MALA. It may occur in association with multiple other

critical medical conditions, such as sepsis, ischemic gut and exposure to gases like carbon monoxide, cyanide hydrogen and hydrogen sulphide.

Our patient presented with profound hypoglycemia and severe lactic acidosis, which required multiple dialysis sessions before the lactate levels gradually decreased. Studies of MALA management always stressed the importance and effectiveness of dialysis as a treatment, especially in renal failure patients^{10,11}.

There are multiple published case reports on metformin induced hypoglycemia. In nearly all, the patients had in common that they were malnourished, performing vigorous exercise, had comorbidities or co-ingestions. Our case is unique in contrast to the other case reports about hypoglycemia in that our patient did not have any co-ingestions, is not diabetic and had the co-occurrence of both MALA and hypoglycemia, which is rare. A review found the occurrence of MALA with hypoglycemia as adverse reaction of Metformin estimated to be 12.5%¹².

CONCLUSION

A diagnosis of metformin-associated lactic acidosis should always form part of the differential diagnosis in patients with a high anion gap. MALA is rare, but it is likely fatal; hence, its identification is vital. It may be difficult to diagnose when a limited history is available. It may occur in patients with renal insufficiency, hemodynamic instability, liver disease, or other illnesses when a high level of metformin accumulates. Treatment of metformin-associated lactic acidosis is supportive, including adequate resuscitation, treating any underlying disease and renal replacement therapy.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None.

Competing Interest: None.

Sponsorship: None.

Acceptance Date: 28 June 2020.

Ethics Approval: Approved by the Research Ethics Committee, Bahrain Defence Force – Royal Medical Services, Bahrain.

REFERENCES

1. DeFronzo R, Fleming GA, Chen K, et al. Metformin-associated Lactic Acidosis: Current Perspectives on Causes and Risk. *Metabolism* 2016; 65(2): 20-9.
2. Von Mach MA, Sauer O, Weilemann LS. Experiences of a Poison Center with Metformin – associated Lactic Acidosis. *Exp Clin Endocrinol Diabetes* 2004; 112:187-90.

3. Lacher M, Hermanns-Clausen M, Haefliger K, et al. Severe Metformin Intoxication with Lactic Acidosis in an Adolescent. *Eur J Pediatr* 2005; 164:362–5.
4. Perrone J, Phillips C, Gaieski D. Occult Metformin Toxicity in Three Patients with Profound Lactic Acidosis. *J Emerg Med* 2011; 40:271–5.
5. Bodmer M, Meier C, Krähenbühl JSS, et al. Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia: A Nested Case-control Analysis. *Diabetes Care* 2008; 31:2086–91.
6. Bolen S, Feldman L, Vassy J, et al. Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. *Ann Intern Med* 2007; 147:386–399.
7. Gong L, Goswami S, Giacomini KM, et al. Metformin Pathways: Pharmacokinetics and Pharmacodynamics. *Pharmacogenet Genomics* 2012; 22(11): 820-7.
8. Silvestre J, Carvalho S, Mendes V, et al. Metformin-induced Lactic Acidosis: A Case Series. *J Med Case Rep* 2007; 1: 126.
9. Kim MJ, Han JY, Shin JY, et al. Metformin-associated Lactic Acidosis: Predisposing Factors and Outcome. *Endocrinol Metab (Seoul)* 2015; 30(1): 78-83.
10. Chang CT, Chen YC, Fang JT, et al. Metformin-associated Lactic Acidosis: Case Reports and Literature Review. *J Nephrol* 2002; 15(4):398-402.
11. Seidowsky A, Nseir S, Houdret N, et al. Metformin-associated Lactic Acidosis: A Prognostic and Therapeutic Study. *Crit Care Med* 2009; 37(7):2191-2196.
12. Renda F, Mura P, Finco G, et al. Metformin-associated Lactic Acidosis Requiring Hospitalization. A National 10 Year Survey and a Systematic Literature Review. *Eur Rev Med Pharmacol Sci* 2013; 17 Suppl 1:45-49.