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Case Report
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Fatal Metformin Poisoning with Associated Lactic Acidosis

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Abstract

Metformin is one of the most widely used anti-diabetic medication. Lactic acidosis although very rare is a serious complication of metformin use. It can be life-threatening with mortality as high as 50% if not recognized and treated early. We report a rare case of fatal metformin poisoning due to severe lactic acidosis following a 40 yr old divorcee with primary infertility secondary to polycystic ovarian syndrome. Treatment of metformin induced lactic acidosis involves the use of renal replacement therapy, sodium bicarbonate infusion and general measures. This case was reported in order to alert physicians on the existence of this rare but life-threatening endocrine emergency. Late presentation was a major limiting factor in the management of this patient.

Keywords: Lactic acidosis; Metformin; Coma; Suicide

Introduction

Metformin, a dimethyl-biguanide, is a widely used oral anti-hyperglycemic agent used in the long-term treatment of Type 2 Diabetes Mellitus (T2DM), polycystic ovarian syndrome and gestational diabetes [1,2]. As a result of its efficacy, safety, lower tendency to Hypoglycemia, cardiovascular and metabolic benefits, it has become the first drug of choice in the treatment of Type 2 Diabetes Mellitus (T2DM) [3,4]. It acts primarily in the liver to reduce blood glucose by decreasing glucose output and, secondarily, in the peripheral tissues mainly in the muscles by increasing glucose uptake [1,5].

Although the most common adverse effects of metformin are mainly gastrointestinal (nausea, vomiting, diarrhea and abdominal discomfort), it also has the potential to cause lactic acidosis. Metformin associated lactic acidosis has been reported even at therapeutic doses in patients with end stage renal disease, heart failure or liver disease [6]. Therefore, caution must be exercised in administering such drugs in those groups of patients.

Studies have not shown any difference between the incidence of lactic acidosis in patients with diabetes taking metformin and those not taking metformin as reported in a meta-analysis of 194 studies by Salpeter et al., it however a recognized complication of metformin use [7]. We present a fatal case of metformin associated lactic acidosis where interactions with benzodiazepines and nicotine may have potentiated the condition that led to the demise of the patient.

Case Presentation

A 40-year-old divorcee diagnosed with primary infertility secondary to polycystic ovarian syndrome, being treated with metformin 1000 mg daily. She was also taking Bromazepam 3 mg daily for clinically diagnosed depression. She was referred to the emergency of our hospital after deliberately ingesting about 100 tablets of metformin (100 g) 48 h earlier in a suicide attempt. At presentation, she was deeply unconscious with GCS of 3/15 on 100% oxygen *via* nasal prong. She had intravenous fluid and later vasopressors. The urethral catheter was *in-situ* and draining less than 50 ml in 12 h and RBS was 122 mg/l. Blood pressure was 70/? mmHg, pulse rate was weak, and all extremities were cold and clammy. Chest findings were wide spread coarse crackles in all lung zones.

No jaundice or bleeding from anybody orifice. She had about three episodes of cardiac arrest and was resuscitated.

Results of laboratory investigations reported a hematocrit of 19.5%, Urea of 2.1 mmol/l, creatinine of 44 mmol/l, potassium of 5.6 mmol/l, bicarbonate of 13 mmol/l, sodium of 141 mmol/l, chloride of 123 mmol/l, whole blood lactate of 16.1 mmol/l normal range (0.5 mmol/l -1 mmol/l), urine toxicology positive for benzodiazepine and cotinine.

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Liver function tests was normal (AST 28U/L, ALT 32U/L, GGT 41U/L, and ALP 169U/L). After about four hours of resuscitation, the patient was confirmed clinically death as she had unrecordable oxygen saturation, fixed and dilated pupils.

Discussion and Conclusion

Lactic acidosis is a rare but life-threatening complication of metformin use and can occur at high doses of administration or at therapeutic doses in the background of end organ damage like, heart liver and kidney failure or in situations of cardiorespiratory compromise [3]. The symptoms of lactic acidosis are non-specific, may include anorexia, nausea, vomiting, abdominal pain, lethargy, hyperventilation, and hypotension. It is clinically characterized by the presence of pH<7.35, blood lactate levels of >2.0 and a PCO_2 of <42 mmHg.

Although metformin associated lactic acidosis is a rare condition, with an estimated prevalence of one to five cases per 100,000 populations, it has a reported mortality of 30% to 50% [3].

Several studies have reported that the prognosis of individuals who develop lactic acidosis from the use of metformin is unrelated to plasma metformin concentration or lactate level [2,3].

Once ingested, metformin is absorbed in the gut via the enterocytes where it is transported to the liver through the portal circulation, in the liver; it causes an increase in the production of lactate by promoting glycolysis and causing a shift from aerobic to anaerobic respiration. Metformin induced lactic acidosis develops when there is an imbalance between increased lactate production and impaired metabolism and/or reduced lactate clearance.

The mechanism of Metformin induced lactic acidosis is due to the impairment of the clearance of lactate via inhibition of complex 1 in the mitochondrial respiratory cycle [3]. Despite the fact that metformin is considered safer than insulin or sulphonylureas due to its lesser tendency to hypoglycemia, the mortality in biguanides (6.1%) overdosing is much higher than overdoses of insulin and sulphonylureas (0.9 and 3.6%) respectively as reported in a study by Von March et al. [8]. Interactions with other drugs like alcohol, benzodiazepines and barbiturates can potentiate the risk of developing lactic acidosis. Therefore, early diagnosis and initiation of intervention in the form of renal replacement therapy is important in order to restore blood lactate levels to normal. This is largely due to the fact that metformin does not bind to plasma proteins and is excreted mainly unchanged in the urine. The index patient presented late as such she could not benefit from the renal replacement therapy.

The type of renal replacement therapy to be instituted depends on the nature of the metformin intoxication. In metformin overdose, Intermittent or continuous renal replacement therapy with Hemodiafiltration is recommended. This has been attributed to the fact that the reductions in the metformin plasma levels have been found to be correlated with improvement of lactic acidosis. Extracorporeal hemodialysis is preferred provided that the patient is hemodynamically stable. Discontinuation of treatment is indicated when lactate levels are lower than 3 mmol/L and pH is higher than 7.35. Hypotension should be treated with intravenous fluids and vasopressors in order to restore the circulatory status to normal. Treatment of acid base disturbances is necessary in order to restore normal cellular function resulting from alterations in the cellular concentrations of Na^+ and Ca^{2+} levels due the pH disturbances. The mainstay in the treatment of acidosis is to target the underlying cause as the use of sodium bicarbonate ($NaHCO_3$-) is controversial. In diseases where there is evidence of $NaHCO_3$- losses, there is clear evidence of the benefit of replacement therapy. There are however no validated clinical studies on $NaHCO_3$- replacement involving patients with lactic acidosis and hemodynamic instability.

At a certain point acidosis has a protective effect in anoxic or ischemic cell, this effect is however lost as the level of acidosis becomes severe. The indications for interfering in acidosis include pH<7.2, HCO_3- <10 mmol/l, and base deficit >10 mmol/l. Mortality in metformin induced lactic acidosis can be as high as 50%, although that is lower than that of other causes of lactic acidosis (50% *vs.* 74%) [9,10]. Therefore, metformin induced lactic acidosis has a better prognosis than other causes of lactic acidosis like sepsis and circulatory failure. Benzodiazepines, when ingested alone are rarely associated with a high mortality or morbidity, but the risk of death rises exponentially when ingested with other drugs especially alcohol, opiates or other sedatives. The risk of death with benzodiazepines is largely due to the fact that they can cause apnea, a risk is highest with alprazolam [6,10]. One of the limitations of our report is the inability to measure serum metformin levels which is not available in our center.

This case was reported in order to alert physicians and care givers on the existence of this rare but life-threatening endocrine emergency. Early detection and institution of appropriate management measures is essential to survival. A Late presentation was a major limiting factor in the management of this patient. This is in addition to the interaction of metformin with benzodiazepines which by themselves can cause lactic acidosis and increased the risk of death of the patient. The inability to measure the serum levels and exclude sulphonyl urea is a major limitation in this study.

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