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CASE REPORT

Life Threatening Lactic Acidosis Secondary To Metformin, In A Low Risk Patient

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ABSTRACT

A 45-year-old lady was admitted to the intensive care unit (ICU) with a two day history of persistent nausea, vomiting, abdominal pain, and shortness of breath. Her medical history was remarkable for diabetes mellitus (DM) type II on Gliclazide 80 mg twice daily, and metformin 500 mg, three times daily. On examination, the patient was tachypnic, with cold extremities. Blood chemistry showed: random blood sugar levels of 20.6 mmol/L, and blood lactate concentration levels of 9.45 mmol/L, while urine and plasma tests were negative for ketone bodies. A provisional diagnosis of metformin-induced lactic acidosis was made. Intravenous calcium gluconate, soluble insulin, and bicarbonate were given initially, and urgent haemodialysis was performed. On the following days, the level of lactic acid and potassium returned to normal. The patient made a subsequent smooth recovery, and did not require further renal support.

Key Words Lactic acidosis, Metformin

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Introduction

Metformin is a useful therapeutic agent for obese type II diabetics, and those whose glycaemia cannot be controlled by sulphonylurea monotherapy. Type B (non-hypoxic) lactic acidosis is an uncommon but potentially fatal adverse effect of metformin. The reported frequency of lactic acidosis ranges between 0.03 and 0.06 per 1000 patient-years, [1-3] mostly in patients with predisposing factors such as chronic renal failure. We report a 45 year old lady who developed life threatening lactic acidosis secondary to metformin, in the absence of pre-existing chronic renal failure or other predisposing factors.

Case History

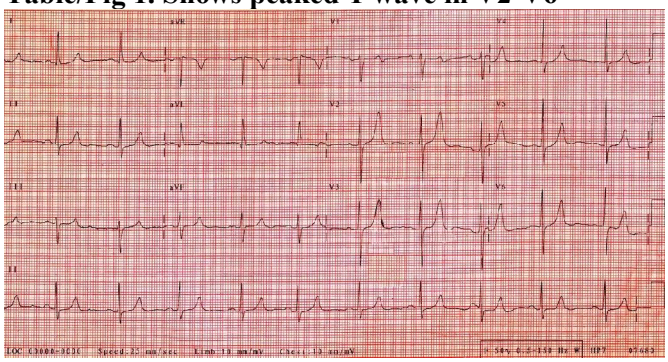
A 45-year-old lady was admitted to the ICU with a two day history of persistent nausea, vomiting, abdominal pain, and shortness of breath. Her medical history was remarkable for DM type 2 on Gliclazide 80 mg twice daily, and metformin 500 mg, three times daily. On examination, the patient was conscious, tachypnic, with cold extremities. Blood Pressure was 100/50 mmHg, Pulse was 110/min, body temperature was 36.3ºC, and respiratory rate was 30/min. Chest, heart, abdomen, and nervous system examination were unremarkable.

Initial investigations showed: haemoglobin level of 14 g/dL, total leukocyte count of 9500/uL platelet count of 467000/uL, blood urea nitrogen levels of 16 mmol/L, creatinine levels of 155µmol/L, sodium levels of 140 mEq/L, potassium levels of 7.5 mEq/L, chloride levels of 109 meq/L, bicarbonate levels of 8 mEq/L, calcium levels of 2.4 mmol/L, random blood sugar levels of 20.6 mmol/L, and blood lactate concentration levels of 9.45 mmol/L. Plasma test for ketone bodies was negative. Liver function test showed: asparate aminotransferase levels of 30 IU/L, alanine amino-transferase levels of 27 IU/L, alkaline phosphatase levels of 70 IU/L, total bilirubin levels of 9 µmol/L, total protein levels of 7.4 g/dL, and albumin levels of 3.8 g/dL. Her coagulation profile was normal. Arterial blood gas analysis at room air showed: pH 6.9, PaO_2 109 mm Hg, $PaCO_2$ 20 mm Hg, and HCO_3^- 7.2 mEq/L. Her fasting lipid profile showed; a total cholesterol level of 5.1 mmol/L; LDL

cholesterol levels of 2.2 mmol/L; triglyceride levels of 3.2 mmol/L. Myoglobin and creatine kinase (CK) levels were normal. The urine was negative for myoglobin, haematuria, pyuria, and ketonuria. An ECG trace showed normal sinus rhythm with peaked T waves (see Figure/Table 1). A review of the patient's biochemical profile, three weeks before admission, revealed normal renal function.

Although metformin level was not measured, metformin and gliclazide were stopped, and the patient was treated as a metformin induced lactic acidosis case. Intravenous calcium gluconate, soluble insulin, and bicarbonate infusion were given initially, and urgent haemodialysis was performed. On the following days, the level of lactic acid and potassium returned to normal. The patient made a subsequent smooth recovery and did not require further renal support; accordingly she was discharged in good condition on subcutaneous insulin.

Table/Fig 1. Shows peaked T wave in V2-V6



Discussion

Metformin is widely used because it has certain advantages over other oral hypoglycaemic agents, namely it does not cause hypoglycaemia, weight gain, or hyperinsulinaemia. [4]

Metformin's mechanism of action is thought to be by increasing glucose transport into glucose utilizing cells, and by decreasing hepatic gluconeogenisis. [4] Biguanide therapy decreases the activity of the enzyme pyruvate dehydrogenase and the transport of mitochondrial reducing agents, and thus enhances anaerobic metabolism[5]. This shift to anaerobic metabolism is therefore not dependant on a lack of oxygen, and in the presence of reduced insulin, increases the production of precursors for the tricarboxylic acid cycle. [5] As inhibition of pyruvate dehydrogenase leads to a decreased ability to channel these precursors into aerobic metabolism, this causes increased metabolism of pyruvate to lactate and an increase in lactic acid production. Any renal impairment will result in a reduced clearance of lactic acid and metformin.

Ninety percent of metformin is excreted unchanged by the kidneys, and lactic acidosis typically occurs in patients with renal insufficiency. [2] Significant renal impairment (serum creatinine >160 µmol/L) is a contraindication to the use of metformin, and mild renal disease increases the risk of lactic acidosis. Metformin is also contraindicated in chronic hepatic disease because of the increased risk of metformin-associated lactic acidosis. Patients with diabetes, frequently have abnormal liver function tests secondary to fatty liver, which in itself is not a contraindication. Other risk factors for metformin-associated lactic acidosis include conditions associated with hypoxia (e.g. recent myocardial infarction, cardiac failure, pulmonary disease and surgery), alcoholism, sepsis, high dosage, increasing age, and dehydration. [6,7] A metformin dosage of 850 mg twice a day, or 500mg three times a day, usually gives good diabetic control. In situations predisposing to dehydration, such as fasting for surgery or contrast radiography, metformin should be ceased at least 48 hours prior to the procedure (or on admission for an emergency procedure), and not restarted until the patient has fully recovered and is eating and drinking normally. The glucose levels of patients in catabolic states, e.g. sepsis or in the post-operative period should be closely monitored, and a short-term insulin therapy should be strongly advised. Caution is needed when increasing the daily dosage beyond 1.7g, especially in the elderly, and those with mild renal disease. Our patient had no obvious risk factor, and had normal renal function three weeks before admission. The mild renal impairment at the time of presentation was due to dehydration caused by severe vomiting.

One study [8] has shown that there is no evidence from prospective comparative trials or from observational cohort studies, that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycaemic treatments, if prescribed under the study conditions, taking into account, the contra-indications. Although this study has significant limitations, it clearly suggests that metformin

might be a less problematic therapy than originally anticipated.
Metformin-induced lactic acidosis is extremely rare in the absence of obvious risk factors. However, there are few cases of metformin-induced lactic acidosis in patients without pre-existing renal failure or other predisposing factors. [9,10]

Signs and symptoms of metformin-induced lactic acidosis are non-specific and include anorexia, nausea, vomiting, altered level of consciousness, hyperpnoea, abdominal pain, and thirst. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

Treatment involves metformin withdrawal, adequate hydration, circulatory support, and correction of the acidosis. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. When it occurs, metformin-induced lactic acidosis is fatal in approximately 50% of cases [2,3,6].

Conclusions

In conclusion, lactic acidosis is a medical emergency that must be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis, even in the absence of obvious risk factors.

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