Metformin associated lactic acidosis: A case report.

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Abstract

Metformin, together with lifestyle intervention, is considered first-line treatment for glycemic management in people with type 2 diabetes. Despite this widespread use, one of the areas of longstanding debate has been whether metformin can be used safely in those with chronic kidney disease (CKD). The concern is the possibility of an increased risk for lactic acidosis resulting from metformin accumulation in those with renal impairment. Metformin associated lactic acidosis (MALA) is a rare complication of long-term metformin therapy and the risk is increased in patients who have concomitant risk factors like cardiac, renal or liver failure. This condition is associated with high mortality and morbidity.

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Introduction

Metformin is a dimethylbiguanide related oral hypoglycemic and is commonly prescribed to treat type 2 diabetes through actions of reducing the hepatic gluconeogenesis and increasing the sensitivity of peripheral tissues to insulin [(1)]. Metformin has a rather good safety profile with gastrointestinal side effects like reduced appetite, nausea and abdominal discomfort being the commonest [(1)]. Lactic acidosis is a rare complication of metformin with an incidence of 3 to 47 per 100000 cases in literature and occurs with long term use of metformin in patients with concomitant risk factors like cardiac, renal or liver failure [(2)]. Here, we present a case of metformin induced severe lactic acidosis in a patient who was on high dose metformin therapy with coexisting impaired renal functions.

Case report

A 65 years old female presented to the emergency department with gradually worsening difficulty in breathing over three days and several episodes of vomiting for two days. She had a reduced appetite for one week which resulted in minimum intake of solids and liquids. There was no evidence of respiratory tract, urinary tract or skin sepsis. She was a known patient with diabetes and dyslipidaemia, for which she was on metformin 1g thrice daily and atorvastatin 20 mg daily for one year. Furthermore, she was found to have stage 3b chronic kidney disease with an estimated glomerular filtration rate (eGFR) of 40 ml/kg/1.73m2.

On examination, she was consciousness, with a GCS 15/15 but severely dehydrated. Her blood pressure was 70/40 mmHg, pulse rate and respiratory rate were 110 /min and 40/ min, respectively. Her respiratory system and abdominal examinations were unremarkable. Her investigations are shown in table 1. Full blood count showed normocytic normochromic anemia. Serum creatinine was 297 µmol/L and blood urea was 70mg/dL. The ultrasound scan of abdomen showed evidence of early renal parenchymal disease. There was evidence of severe high anion gap metabolic acidosis with a pH of 6.9, bicarbonate 2.4 mmol/L, lactate 11.2 mmol/L and base excess 26 in her arterial blood gas analysis. Her liver functions were normal. Troponin, septic screening and urine ketone bodies were all negative.

Table 1

Variable	Patient's Value
Complete blood count	
White cell count	8.5x 109 /mm3 (Neutrophil 76%)
Platelet	229,000/mm3
Haemoglobin	10.1 g/dL
Renal functions tests	
Serum Creatinine	297 umol/L
Blood Urea	70 mg/dL
Serum electrolytes	
Na+	130 mmol/L
K+	5.5 mmol/L
Liver enzymes	
AST	34 IU/L
ALT	32 IU/L
Random blood sugar	196 mg/dl
Urine ketone bodies	Negative
Arterial blood gas	
pH	6.9
Lactate	11. 2 mmol/L
HCO3-	2.4 mmol/L
Chloride	96 mmol/L
pCO2	18 mmHg
pO2	90 mmHg
Base excess	26 mmol/L
Inflammatory markers	
C-reactive protein	< 5 mg/L
Erythrocyte sedimentation rate	25 mm/1st hour
Septic screening	
Urine culture	No growth
Blood cultures	No growth
Clotting profile	
PT/INR	1.0
aPTT	32 seconds
Cardiac markers	
Troponin	Negative
ECG	Sinus tachycardia. No ischemic changes

On admission, fluid resuscitation was carried out with boluses of crystalloids 20ml/kg due to her hypotension. Subsequently, a noradrenaline infusion was initiated at a rate of 0.1ug/kg/min and was titrated to a maximal dose of 4ug/kg/min combined with dobutamine at a rate of 20ug/kg/min aiming to achieve a desirable mean arterial pressure (MAP) for hemodialysis. Moreover, intravenous sodium bicarbonate (8.4%, 300ml) was given to correct acidosis. Unfortunately, she expired four hours after admission despite vigorous resuscitation.

Discussion

Lactic acidosis is a rare complication of metformin. Its incidence varies from 3 to 47 per 100000 cases in different case series [2]. Phenformin, which was a drug in the biguanide class was withdrawn from clinical practice in the late 1970s due to discovery of increased potential risk of phenformin related lactic acidosis. Metformin induced lactic acidosis (MILA) is described in medical literature as lactic acidosis that cannot be explained by any other risk factor other than the long-term metformin usage leading to drug accumulation in the body [3]. In comparison, Metformin associated lactic acidosis (MALA) refers to a clinical scenario where lactic acidosis is seen in patients who are on long term metformin but also have concomitant risk factors such as cardiac, renal or liver failure which may contribute to lactic acidosis [2].

Our patient had a severe high anion gap metabolic acidosis with an elevated lactate level. She was found to have renal dysfunction one year ago, despite this finding she was started on a high dose of metformin and continued for a duration of one year without any monitoring of her blood sugar levels or renal functions. At the time of the presentation to the hospital she did not have clinical or biochemical evidence of sepsis, cardiac dysfunction or liver failure which could otherwise provide an alternative explanation for severe metabolic acidosis with circulatory failure. As her random blood sugar level was within the normal range and her urine ketone bodies were negative, diabetic ketoacidosis seemed to be an unlikely cause for her clinical presentation. Therefore, it was agreed upon that long-term metformin therapy while having significant renal impairment contributed to the severe lactic acidosis in our patient.

As metformin is excreted by kidneys via tubular secretion, an impaired renal function would contribute to accumulate it in the body especially, if continued at higher doses [1]. These excess methylbiguanide molecules act on the cellular mitochondria in hepatocytes and impair the body's most efficient energy producing pathway i.e. aerobic metabolism and oxidative phosphorylation[5]. This inhibition promotes anaerobic metabolism which produces lactates in excess. Lactate, when produced is predominantly cleared from the circulation by the liver through a concentration dependent mechanism, while 20% is cleared by the kidneys.

Lactic acidosis is two types [2]. Type A is due to tissue hypoxia seen in conditions such as severe anemia, shock, cardiac failure and carbon monoxide poisoning. Non hypoxic conditions like liver or renal dysfunction, severe sepsis and drugs causing increased production of lactic acid is categorized as type B. As evidenced by the above clinical scenario, our patient was suffering from type B lactic acidosis due to high unregulated metformin dosing and renal dysfunction. Lactate has a negative ionotropic effect on the myocardium [5]. This may have contributed for her low blood pressure. Furthermore, lactate can increase the release of endothelial derived nitrous oxide (eNO) a potent vasodilator, especially in the presence of significant sepsis [4] which may have further contributed to lower her blood pressure.

The maximum approved daily dose of immediate release metformin and extended release metformin in the absence of other comorbidities is 2550mg and 2000mg, respectively [6]. However, our patient was started on a supratherapeutic dose (3g daily in divided doses) and continued without monitoring her renal functions. Even though the usage of metformin in mild to moderate renal dysfunction is recommended provided the renal functions are regularly monitored, the recommendations for metformin usage in severe renal impairment seem to be equivocal among different clinicians and institutions, as long as the eGFR is greater than 30 mL/min/1.73 m2 [7]. Canadian Journal of Diabetes suggests rational dosage adjustment for patients with eGFR between 30 and 60 mL/min/1.73 m2, specifically 1.5 g daily for CKD stage 3A and 1 g daily for CKD stage 3B [2,7]. Furthermore, they suggest that low-dosage metformin (500 mg once daily) may be safer in patients with eGFRs between 15 and 30 mL/min/1.73 m2 [7]. In our patient, metformin may have been commenced when eGFR was greater than 30 mL/min/1.73 m2 but dose adjustments were not made to the rising creatinine or falling eGFR as she was not being followed up regularly.

MALA has many etiologies. One or more of these etiologies directly and/or indirectly can contribute in predisposed patients. Cardiac, pulmonary and liver failure are important risk factors for MALA [2]. Furthermore severe dehydration, severe sepsis, advanced age and coadministration of angiotensin converting enzyme inhibitors (ACEI), nonsteroidal anti-inflammatory drugs (NSAIDs) and antiretroviral drugs are also recognized risk factors [2]. Our patient however, was started on a high dose of metformin (well above the recommended daily dose), was continued on the same dose while she had evidence of early chronic kidney disease, and her disease status was not monitored thereafter. She was severely dehydrated on admission. All these factors played a significant role in the final clinical outcome of our patient. Although serum lactate levels and metformin levels need to be measured for a definite diagnosis of MALA, serum metformin measurement is not widely available and is expensive. Therefore, this was not performed in our patient.

High index of suspicion along with early detection and prompt treatment of MALA is essential for a positive outcome. Under-diagnosis and high mortality may be the reason why MALA is only seen very rarely. Even if treated

in an intensive care unit (ICU) setting the mortality is as high as 50% [5]. A low pH with a high lactate value & a high metformin concentration are predictors of poor prognosis. Patients who are suspected of having MALA do not have disease specific symptoms or signs but will present with generalized malaise and gastrointestinal disturbances, hypotension, hypothermia, altered sensorium, reduced urine output and in some patients, hypoglycemia. Clinicians need to have judicious decision making when a patient presents with a suggestive clinical picture.

The definite treatment of MALA is hemodialysis which will effectively remove the toxic metformin molecules as well as excess lactates in the body [3]. If performed promptly, it will reverse the inhibition exerted on mitochondria by the metformin molecules correcting acidosis. Hemodialysis will also help in removing other toxic substances especially if there is a concomitant acute kidney injury. Unfortunately, our patient was not haemodynamically stable enough to undergo hemodialysis despite vigorous resuscitation and ionotropic support. The prognosis of lactic acidosis primarily depends on the underlying mechanism and on its reversibility [6]. The benefits of using sodium bicarbonate to treat lactic acidosis is limited by its ability to induce intracellular hypercapnic acidosis, hypoglycemia and a significant decrease in ionized calcium, all of which can aggravate the condition of the patient [5]. Therefore, the use of sodium bicarbonate to treat lactic acidosis should be done with extreme caution. The situation can be much more complex and less easily reversible when lactic acidosis is primarily due to severe hypoxia or tissue hypoperfusion.

Conclusion

Lactic acidosis is a rare complication of metformin therapy. Despite having a high mortality, this should not discourage the use of metformin to treat patients with diabetes as the benefits are well established and overweighs the remote risk of lactic acidosis. But it is of utmost importance to closely monitor the renal functions and make appropriate dose adjustments accordingly. Prompt detection and early intervention with supportive therapy and renal replacement therapy can produce a favourable outcome in patients with metformin associated lactic acidosis.

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