Case Report:

Metformin-associated lactic acidosis: it really happens!

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ABSTRACT

Metformin-associated lactic acidosis (MALA) in the absence of other risk factors, is extremely rare. A 60-year-old male presented to the emergency department feeling tired and breathless for the preceeding 3 days. He had a 10 year history of type 2 diabetes mellitus (T2DM) and was receiving treatment with metformin. There was no history of fever, cough or orthopnoea. Physical examination was unremarkable. Arterial blood gas analysis showed an increased anion gap metabolic acidosis and raised lactate. Mild pre-renal impairment was also present. There was no evidence of sepsis, heart or liver failure, anaemia or history of alcohol abuse. He received intravenous fluids with resultant normalisation of renal function but lactate levels remained elevated and bicarbonate remained low. At this point a diagnosis of MALA was considered. Metformin was stopped and within 24 hours lactate and bicarbonate levels returned to normal limits. This case highlights the possibility of metformin-treated patients developing lactic acidosis in the absence of other risk factors. Any unwell patient taking metformin should undergo measurement of serum lactate and bicarbonate.

Key words: *Metformin, Lactic Acidosis*

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INTRODUCTION

Metformin is advocated as first line therapy for type 2 diabetes. Metformin-associated lactic acidosis (MALA) has an incidence of 1-5 cases /100,000 person years and is a rare complication.[1] However, given the large number of patients taking this drug in India, this complication deserves attention due to its high mortality if unrecognised. We present the case of a patient who developed MALA and made a full recovery.

CASE REPORT

A 60-year-old male patient with type 2 diabetes mellitus for the last 10 years who was receiving oral metformin (2 g/day), presented to us with easy fatiguability and breathlessness at rest of 3 days duration following two episodes of vomiting. There was no history of fever, cough or orthopnoea. He had vomited large volumes of clear fluid; there was no diarrhoea. He was known to have chronic obstructive pulmonary disease and pulmonary hypertension, for which he was on treatment with bronchodilators. He did not consume alcohol, and had stopped tabacco smoking 4 years ago.

On arrival to the emergency department, his pulse and blood pressure were normal; respiratory rate was 36/min. Systemic examination was unremarkable except for mild dehydration. His chest was clear on auscultation and oxygen saturation was 98% on room air. The chest radiograph was normal. Arterial blood gas (ABG) analysis revealed high anion-gap metabolic acidosis with pH 7.31; serum bicarbonate of 9 mEq/L. Serum lactate was high

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(45·5 mg/dL) (normal range 5-22 mg/dL). Liver function tests were normal. Urine ketones were negative.

He also had mild pre-renal failure (blood urea of 56 mg/dL; serum creatinine of 1·6 mg/dL). No obvious cause of metabolic acidosis was found. Metformin plasma levels could not be measured as it was unavailable. Sepsis did not seem likely, Total leucocyte count was 9600 cells/mm^3 and peripheral smear also was normal. Echocardiography was normal except for moderate pulmonary hypertension.

He was given 100 mL of 1.26 % sodium bicarbonate and hydrated with intravenous (IV) fluids. On the next day he was better clinically and serum creatinine became 1mg/dL. But his acidosis persisted. The possibility of MALA was considered, metformin was withheld and insulin was started. Repeat measurement of lactate and bicarbonate improved to 8 mg/dL and 20 mEq/L respectively and acidosis resolved within next 24 hours as summarised in Table 1.

DISCUSSION

MALA is a type B lactic acidosis, recognized as a potentially lethal condition that can occur in patients with contraindications to the drug such as renal failure, sepsis, hypoxaemia, and alcoholism.[2] Usually MALA occurs with therapeutic dosage of metformin with any of the above risk factors or due to drug over dosage. In our patient mild renal failure was the only risk factor which occurred due to dehydration following vomiting. Sepsis, hypoxia, and infection were ruled out.

It has been reported that 89·8% patients who developed MALA had at least one risk factor for occurrence of lactic acidosis and renal failure was present in almost 50% of the patients.[3] Clinical features of MALA can be vague.[4] Our patient had presented with extreme weakness and vomiting. Our patient satisfied the Luft criteria for lactic acidosis, namely, pH < 7·35 and lactate > 45mg/dL.[5] Metformin levels could not be measured, but since all other causes of increased lactate were ruled out, MALA was diagnosed.

Surprisingly, the pH and lactate levels do not correlate with worse prognosis. Most patients with MALA survive despite a very low arterial pH and lactic acidosis due to MALA, though severe is associated with better prognosis than due to sepsis. The reason for this difference could be the protective effects of metformin in patients with shock, with vasomotility benefits.[2]

Our patient had low pH and high lactate, but improved very well on stopping metformin. The prognosis is partially affected by host factors and comorbidities such as renal failure, hypoxia, and hypotension.[6] Since MALA is associated with high mortality, early recognition and stoppage of drug is crucial.

The treatment consists of prompt stoppage of the drug and correction of pH with bicarbonate if it is low. Dialysis will correct the acidosis and remove metformin and help clearing further lactate formation. Our patient recovered in 48 hours with simple measures, of stopping the drug and rehydration.

This case highlights the possibility of metformin-treated patients developing lactic acidosis in the absence of other risk factors.

Table 1: Serial measurements of biochemical parameters

Biochemical Parameters	Day 1	Day 2	Day 3
Serum $HCO3^-$ (mEq/L)	9	13	20
Plasma Lactate (mg/dL)	45·5	32·4	8
pH	7·31	7·41	7·45
Serum creatinine (mg/dL)	1·6	1·1	0·9

HCO_3^- = bicarbonate

Any unwell patient taking metformin should undergo measurement of serum lactate and bicarbonate.

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