

Unexpected survival from severe metformin-associated lactic acidosis

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ABSTRACT

Lactic acidosis is a recognised complication of the anti-hyperglycaemic biguanide agent metformin, especially in patients with renal failure. We report a case of severe lactic acidosis and hypothermia due to metformin treatment and renal impairment. The favourable outcome despite extremely unfavourable clinical signs and symptoms for survival after admission and initial treatment was unexpected. Specific aspects of the clinical course are addressed.

INTRODUCTION

Oral hypoglycaemic medications are often used in hyperglycaemic patients. Metformin, the only available biguanide compound in the Netherlands, is frequently used in type 2 diabetes mellitus patients. Phenformin, another biguanide, was withdrawn in several countries because of its association with lactic acidosis and related mortality.¹

Although lactic acidosis is reported less frequently with metformin than phenformin, it can be considered a serious and life-threatening adverse event.² In the present case we report the unexpected survival of an extreme case of metformin-associated lactic acidosis (MALA).

CASE REPORT

A 72-year-old woman was admitted to the hospital because of severe dyspnoea. Her medical history revealed diabetes mellitus for 15 years with diabetic nephropathy for five

years (albuminuria 264 mg/l, Cockcroft estimated creatinine clearance 28 ml/min), adequately treated hypertension for the last four years and cerebrovascular accidents (TIA, minor stroke) three years ago without major lasting sequelae.

On admission she was unable to give additional information due to her clinical condition. Family members confirmed the existence of rapidly progressive dyspnoea. She had been anorectic for three days and had not drunk at all. Furthermore, during the three days before admission, she had developed a cough with purulent sputum and severe diarrhoea. A general practitioner prescribed doxycycline. Other medication consisted of enalapril 20 mg tid, metformin 850 mg tid, glibenclamide 5 mg tid, dipyridamole 75 mg qid and aspirin 30 mg. Family members confirmed that patient had not been taking all her medications.

On physical examination the patient appeared to be severely ill. The skin was cool and clammy and capillary refill was slow. Respiratory rate was 40/min. Heart rate was 82 beats/min and arterial blood pressure 120/70 mmHg, rapidly deteriorating to 85/25 mmHg within one hour, despite fluid resuscitation. Core body temperature was 33.8°C and dropped to 32.6°C. EMV score was 3. Pupillary reactions were slow. Physical examination was otherwise unremarkable.

An arterial blood sample showed: pH 6.67 (7.35 to 7.45), pCO₂ 1.7 (4.5 to 6.0 kPa), pO₂ 29.9 (9.5 to 13.0 kPa), HCO₃ 1.4 (22 to 26 mmol/l), BE -27 (-2 to +2), and O₂ saturation 97 (92 to 99%). Venous lactate was 12.6 mmol/l (0.5 to 2.2). Other laboratory results were: CRP 37 (<5 mg/ml), Hb 6.8 (7.5 to 10 mmol/l), leucocytes 14.3 (4 to 11/nl), sodium 144 (135 to 145 mmol/l), potassium

5.9 (3.5 to 5.0 mmol/l), creatinine 986 (50 to 90 $\mu\text{mol/l}$), urea 33.3 (3 to 7 mmol/l), glucose 15.1 (4.0 to 10.0 mmol/l) and CK 56 (0 to 170 U/l). Liver enzymes were within normal ranges. Metformin levels were not measured. A chest X-ray showed no abnormalities. An electrocardiogram revealed sinus rhythm and left bundle branch block. An abdominal ultrasound excluded post-renal obstruction and showed no evidence of intra-abdominal pathology. To exclude a septic aetiology, cultures were taken from blood, tracheal aspirate and catheter urine, and empirical treatment with cefotaxime and gentamicin was started. All cultures remained negative.

The patient was admitted to the Intensive Care Unit. Admission was immediately followed by cardiac arrest; cardiopulmonary resuscitation was successful. Circulatory shock resulted and vasopressors and inotropes were started and increased to maximal levels at dopamine 25.3 $\mu\text{g/kg}^{-1}/\text{min}^{-1}$, dobutamine 8.4 $\mu\text{g/kg}^{-1}/\text{min}^{-1}$, noradrenaline 1.05 $\mu\text{g/kg}^{-1}/\text{min}^{-1}$, and adrenaline 0.04 $\mu\text{g/kg}^{-1}/\text{min}^{-1}$. Suspected vasopressin deficiency was treated with terlipressin 1 mg bolus iv.

For (supra)ventricular tachycardia, amiodarone was continuously infused restoring sinus rhythm. Hypothermia was treated with external rewarming and resuscitation with nine litres of fluids in the first 24 hours.

Corticosteroid, thiamine and insulin suppletion were commenced. Acidosis was corrected by artificial hyper-ventilation by means of mechanical ventilation and continuous sodium bicarbonate infusion of 1200 ml 8.4% over 12 hours. As a result serum sodium levels rose to 178 mmol/l and chloride to 109 mmol/l. Arterial lactate levels increased to 33.8 mmol/l.

Physical examination after 16 hours showed an EMV score of 3 and absent pupillary reactions. After 24 hours an APACHE II score of 39 was calculated.

Optimal neurological prognostic estimation was complicated if not impossible due to severe hypernatraemia and catecholamine infusion. Therefore, a decision to continue full treatment was made. Anuria persisted and continuous veno-venous bicarbonate-buffered haemofiltration (CVVH, 48 litres replacement fluid) was started. Serum bicarbonate, pH and sodium levels were within normal ranges 24 hours after initiation of CVVH. Within 48 hours all neurological functions returned to normal. Circulatory shock resolved. The patient was transferred to the Department of Internal Medicine and Nephrology after 11 days. After one month renal failure still existed and intermittent haemodialysis was continued.

DISCUSSION

Susceptibility to MALA is not completely understood. Previous data have suggested that metformin is not

associated with an increased risk of lactic acidosis compared with other antihyperglycaemic treatments in patients in which metformin contraindications have been respected. Nevertheless, in patients with possible risk factors, which may potentiate the lactacidaemic effect of metformin, MALA has been described before (*table 1*).^{2,3}

Table 1

Practical recommendations to minimise risk of MALA²

AVOID USE OF METFORMIN

Serum creatinine >135 $\mu\text{g/l}$ (men), 110 $\mu\text{g/l}$ (women) or creatinine clearance <50 ml/min

Septicaemia

Acute myocardial infarction/congestive cardiac failure/shock

Abnormal liver function tests suggestive of impaired liver function

Alcohol abuse

Metabolic acidosis

Surgery

Pregnancy

LIMIT/REVIEW USE OF METFORMIN

Chronic stable cardiac failure

Vitamin B12 deficiency

Intravascular radio-contrast studies

Elderly patients (>80 years)

In the USA the reported rate of confirmed biguanide-associated type B lactic acidosis is three cases per 100,000 patient-years.² Because many diabetes mellitus patients are treated with metformin, a large group is at risk of developing MALA.

In our case other causes of lactic acidosis, such as sepsis, thiamine deficiency, acute liver failure or hypoxaemia, were excluded. The patient continued high-dose metformin treatment up to admission. Therefore, it seems highly likely that the observed clinical picture is due to MALA, although metformin levels were not measured. On the other hand, accumulation of metformin does not correlate with lactate concentrations or mortality and metformin levels would therefore probably be of limited value.⁴ Profound severe metabolic acidosis in the absence of hypoxaemia should raise the suspicion of type B, potentially reversible lactic acidosis.⁵ The severe renal failure probably contributed to the severe metabolic acidosis. Renal insufficiency should be considered the most likely predisposing factor in the development of this case of severe MALA. In fact, the high-dose metformin (2550 mg a day) should have been withdrawn earlier based on the impaired renal function. Contraindications are often neglected in clinical practice. In a study among patients on metformin

therapy who were admitted to hospital, 27% had specific contraindications for its use. Of these contraindications renal insufficiency was most frequently observed.⁶ Attributable factors for severe renal failure identified in our patient were the diabetic nephropathy combined with reduced fluid intake and water loss due to a probable upper respiratory tract infection and severe diarrhoea causing prerenal failure further aggravated by the use of an angiotensin-converting enzyme inhibitor. Furthermore, in hypothermic patients major fluid losses have been observed.

The relation of MALA and hypothermia is unclear but another case with similar comorbidity and aetiology has been described in the literature.⁷

ACE inhibitor therapy affects glomerular autoregulation by intrarenal efferent vasodilation with a consequent fall in filtration pressure. In case of reduced renal perfusion due to dehydration, marked reductions in glomerular filtration rate may be observed. In such cases the withdrawal of ACE inhibitor treatment is warranted.⁸

In elderly patients, especially those with vascular disease, dehydration and drug-related causes of renal failure are more often associated with mortality and prolonged renal replacement therapy.⁹

The survival of our patient is remarkable because severe MALA is associated with poor outcome. In a study of 330 patients with biguanide-associated lactic acidosis, only eight had a normal plasma creatinine at the time of diagnosis. The mean blood lactate was 16.9 mmol/l and the mortality about 50%.¹⁰ In cases of MALA with a pH <6.9 with raised urea and a lactate >18 mmol/l prognosis is extremely poor.¹¹ In 126 MALA patients, all nine patients with an APACHE II score above 30 died within 24 hours.¹² The APACHE II score in our patient was 39. In our case, neurological signs and symptoms were predictive of poor outcome. Initial neurological evaluation was complicated by hypothermia and later by severe hypernatraemia due to infusion of sodium bicarbonate. During hypothermia, inotropes and catecholamine infusion and severe hypernatraemia, pupil size and reactions to light are difficult to interpret.¹³ Hypothermia may have prevented further neurological deterioration after the initial cardiopulmonary resuscitation. Mild hypothermia (12 to 24 h of 32 to 34°C) in comatose patients has been shown beneficial for the neurological outcome even in patients with obvious noncoronary causes for cardiac arrest.¹⁴ Initially, the treatment strategy was focused on the optimisation of fluid status to correct for hypovolaemia and prerenal failure as well as the reduction of acidosis. However, the supply of sodium bicarbonate had to be stopped because the concentrations of plasma sodium became severely elevated as has previously been described in the literature.¹⁵ After the initiation of CVVH sodium, the bicarbonate levels and pH rapidly normalised.

Therefore, in our opinion as well as others,¹⁶ the early institution of bicarbonate-buffered CVVH is warranted in renal failure associated severe MALA and should be preferred above infusion of sodium bicarbonate alone. In conclusion, although severe MALA has been proven to have a poor prognosis in general, interpretation of clinical neurological signs and prognostic estimations based on lactate, bicarbonate levels or APACHE II scoring should be interpreted with caution in individual cases. Hypernatraemia due to sodium bicarbonate infusion can be limited by using early institution of continuous bicarbonate-buffered renal replacement therapy. Furthermore, adherence to known exclusion criteria in the prescription of metformin is stressed by this case of extreme MALA.

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