

Lactic acidosis due to metformin therapy in a low risk patient

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Summary: A 55 year old diabetic woman treated with chlorpropamide and metformin for three years presented with acute oliguric renal failure and lactic acidosis from which she died. The plasma metformin level was very high suggesting that the lactic acidosis was caused by the drug. There were no contraindications to metformin therapy and renal function was normal three months previously. This case demonstrates that lactic acidosis can occur as a result of metformin therapy in the absence of pre-existing risk factors.

Introduction

Previous reports of lactic acidosis associated with metformin therapy are confined to patients with pre-existing renal failure, liver disease, or excessive alcohol ingestion.^{1,2} We report a case of fatal lactic acidosis in a patient with no identifiable risk factor.

Case report

A 49 year old woman presented in 1978 with Type II diabetes. She weighed 56 kg (ideal body weight 58 kg) and was successfully treated with diet, glibenclamide and metformin. In 1983 postprandial plasma glucose levels were 14.5 and 10.7 mmol/l and her weight was 46 kg, but she refused advice to change to insulin therapy. Her treatment was chlorpropamide 500 mg daily and metformin 850 mg t.d.s. In March 1984 she complained of tiredness and her haemoglobin was 11.0 g/dl, mean corpuscular volume (MCV) 112 fl (normal 75–95), serum vitamin B₁₂ 57 ng/l (normal >150 ng/l) and serum folate normal. Plasma urea was 4.8 mmol/l (normal 3.0–6.5) and plasma creatinine was 91 μmol/l (normal 60–125). Serum intrinsic factor antibody was not detected and serum haptoglobin was present in normal amounts. She declined further investigation. Three months later she presented with anorexia, weight loss, thirst, dyspnoea and tingling of the extremities. Depression and excessive alcohol intake were

denied. Examination was normal, her blood pressure was 130/70 mmHg and capillary blood glucose was 10 mmol/l. Plasma electrolytes were normal but the plasma creatinine was 155 μmol/l rising to 347 μmol/l on the following day. These results were not available until she was admitted to hospital after a syncopal attack two days later. On examination she was drowsy, pale and peripherally cyanosed with a pulse rate of 80/min and systolic blood pressure of 90 mmHg. Plasma concentrations were: glucose 0.8 mmol/l, lactate 16.8 mmol/l (normal 0.6–2.4), sodium 133 mmol/l (135–145), potassium 6.0 mmol/l (3.5–5.0), bicarbonate 6.0 mmol/l and urea 29.6 mmol/l. Arterial blood gas analysis revealed: pH 7.027, P_{CO₂} 2.55 kPa, P_{O₂} 19.11 kPa, HCO₃ 4.7 mmol/l. Liver function tests were normal. Haemoglobin was 8.1 g/dl, MCV 120.5 fl (normal 75–95), serum B₁₂ 49 ng/l (normal >150) and red cell folate normal. The plasma metformin level was 56.8 μg/ml (normal mean therapeutic level <5.0). Urine output was 350 ml in 24 hours. Despite correction of the hypoglycaemia and acidosis, treatment with peritoneal dialysis and the use of inotropic agents, the patient deteriorated and died 36 hours later. Post-mortem examination revealed evidence of a mild degree of recent renal tubular damage but no hepatic, cardiac or any other significant abnormality.

Discussion

The very high plasma metformin and lactate levels indicate that the terminal event in this patient was metformin-induced lactic acidosis. The development

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Accepted: 27 October 1987

of acute renal failure immediately prior to its onset may have led to the metformin accumulation. However no cause for the renal failure was found and in particular it preceded the development of shock. An alternative possibility is that the acute renal failure was related directly to metformin toxicity. Although metformin has not previously been reported to be nephrotoxic, acute renal failure and lactic acidosis have been reported to develop comparatively easily in metformin treated patients who had previously normal renal function, in association with gastroenteritis, intravenous pyelography or with diuretic therapy.³ Also some patients with apparent chronic renal failure at the onset of lactic acidosis have been shown to achieve almost normal plasma creatinine concentrations after treatment and withdrawal of the biguanide, suggesting that there may be a contributory drug effect.⁴ In this patient the low vitamin B₁₂ and macrocytic anaemia were possibly also related to the metformin which may have induced B₁₂ malabsorption,⁵ as there was no evidence of haemolysis, folate deficiency or of pernicious anaemia.

The development of hypoglycaemia on the day of admission was probably due to the fact that the patient had taken chlorpropamide on that day and was not eating. This was corrected easily with

intravenous dextrose and did not recur. The dose of metformin used in this patient is within the recommended maximum dosage of 3g/day (British National Formulary, 1987) and is unlikely to have contributed directly to the development of lactic acidosis. The possibility that the patient took an overdose of metformin cannot be excluded, but there was no evidence to suggest this.

There have been no reports of lactic acidosis due to metformin after 56,000 patient years of its use in Canada,⁶ and there is only one previously reported case in the United Kingdom, which occurred in a patient who abused alcohol.² Our case is exceptional but demonstrates that metformin-induced lactic acidosis may occur in a patient with no recognised contraindication to its use. Furthermore regular screening of renal function in this patient would not have been helpful. This case suggests that patients who are underweight and likely to be insulin deficient may be at particular risk from lactic acidosis.

Acknowledgements

We are grateful to Simbec Research Limited for the analysis of plasma metformin.

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