Case Report

Metformin Overdose: A Case Report

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ABSTRACT

Metformin is widely used in the treatment of type 2 diabetes. Overdose with this drug in children may cause profound, wide anion-gap metabolic acidosis and may be potentially lethal. After correction of circulation deficits, bicarbonate replacement may be sufficient for the treatment of acidosis, and there may be no need for haemodyalisis. A case of a teenager is reported in this paper who ingested one of the largest amounts of metformin reported in the literature in a suicide attempt.

Key Words: *metformin, paediatric, lactic acidosis*

Introduction

Metformin, a biguanide derivative, is widely used in the treatment of type 2 diabetes. Although it has been in use in Europe, Canada, and other countries since the 1970s, it was approved for use in the U.S. only from 1995. The primary reason for the delay was the risk of lactic acidosis associated with the use of an earlier biguanide, phenformin[1]. Metformin acts as an insulin-sensitising agent, inducing greater peripheral uptake of glucose, as well as decreasing hepatic glucose output. It also decreases gluconeogenesis from alanine, pyruvate, and lactate, and the accumulation of lactic acid may intensify under certain circumstances[2]. Lactic acidosis is a rare but serious complication of metformin and may develop in overdose, or in the presence of renal impairment or circulatory failure. Only a few cases of deliberate self-poisoning with metformin have been described in the literature[3]. A case of metformin intoxication with profound gap acidosis, hypoglycaemia, and convulsions is presented.

The Case

SA, a 16-year-old girl who took a large dose of her mother's metformin tablets in a suicide attempt was referred to the emergency department of our university hospital. Although the exact quantity of tablets taken was not known, the ingested dose of metformin was estimated to be about 25 grams on the basis of interview and scene investigation. She had been admitted to the local government hospital complaining of headache and confusion, and had had an episode of tonic-clonic seizures at that hospital. On development of severe hypoglycaemia, she was referred to our hospital. On admission she was found to be stuporous. Pulse rate was 102/min, systolic blood pressure: 80 mmHg, axillary temperature: 36ºC, respiratory rate: 32 per minute, and capillary filling time was 3 seconds. The patient had been previously well and had no past medical history of diabetes or renal impairment. She had not taken any other prescribed or illicit drugs. Initial investigations revealed normoglycaemia (glucose: 96mg/dl). Blood gas analysis revealed the following: pH - 7.02, PaO_2 - 182.3 mmHg, $PaCO_2$ - 10.1 mmHg, bicarbonate - 7.2 mmol/l, and anion gap was 47.7 mmol/l. Electrolytes and liver profile were within normal limits. Serum urea was 23 mg/dl and creatinine 2.5 mg/dl. Electrocardiogram and chest X-ray were normal.

Initial treatment included fluid resuscitation with normal saline, dopamine infusion at a rate of 10mcg/kg/minute, gastric lavage, and activated charcoal. Subsequently, bicarbonate replacement was begun, and a total of 300 mEq bicarbonate was infused over the next 6

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hours. Afterwards, the patient appeared to recover, and acidosis started to resolve. There was deterioration in her serum urea and creatinine to 47 mg/dl and 3.3 mg/dl respectively on day 3, which however normalised by day 6. The patient was discharged from hospital on the 7th day of admission. During one month of follow up at out patient clinics no complications have been noted.

Discussion

Metformin is a widely used oral hypoglycaemic agent in diabetes mellitus. Deliberate self-poisoning with oral hypoglycaemic agents is relatively uncommon. There are very few large studies, case series, or case reports of metformin ingestion in children. A multicenter study including 55 paediatric cases, with up to 1700 mg metformin ingestion in healthy children was found not to pose a significant risk. But in this study the maximum ingested dose of metformin was 16.5 grams, which is very low compared to the amount ingested by our patient (25.5 grams).[9] In that sense, our patient represents one of the highest doses of metformin intoxication of childhood ever reported.

In our patient, though the blood lactate level could not be measured due to technical reasons, the presence of profound metabolic acidosis with a very high anion gap (46 mmol/L) implied lactic acidosis. The patient was also hypotensive and had poor circulation. It is possible that the concurrent circulatory problem resulted in increased lactate production, which exacerbated acidosis. Metformin associated lactic acidosis is rare, and is estimated to be 2-3 cases per 100,000 person-years among diabetic patients treated with metformin.[6] In one of the cases reported in literature, a patient who ingested a large quantity of metformin and other drugs suffered from shock, lactic acidosis, and hypoglycaemia, before succumbing.[10] Mortality in most of the cases with metformin associated lactic acidosis is the result of renal insufficiency, hepatic dysfunction, or clinical condition associated with tissue hypoxia or hypoperfusion.[11,12] Although at the time of admission, our patient had hypoperfusion, a factor that could worsen the outcome in metformin intoxication, management with proper fluid resuscitation and inotropic medication prevented the development of profound acidosis. After correction of circulation deficits, bicarbonate replacement was sufficient in reversing the acidosis, and there was no need for haemodialysis.

With biguanides, the main risk appears to be cardiovascular collapse secondary to profound acidosis.[13] The management of biguanide overdose is largely supportive and directed at correcting the metabolic acidosis along with associated complications. Another important point is the presence of hypothermia in metformin intoxication.[14] Our patient was also hypothermic at admission with an axillary body temperature of 36ºC. Although the exact cause of hypothermia is not clear, it could be due to poor circulation.

The use of bicarbonate in hypoxic lactic acidosis has not been shown to be beneficial from a haemodynamic standpoint, and it may in fact worsen intracellular acidosis and exacerbate hyperlactaemia.[15,16] In our patient, after correction of circulation by fluid resuscitation with normal saline and dopamine infusion, bicarbonate replacement was begun and proved successful. The use of venovenous haemofiltration against a non-lactate containing fluid may improve outcome when sodium bicarbonate alone fails to reverse severe systemic acidosis.[14] Unlike sulfonylurea agents, the mechanism does not involve stimulation of insulin secretion by the endocrine pancreas, and hypoglycemia is generally not expected. But our patient had a hypoglycaemic attack.

In conclusion, metformin intoxication with high doses in children may cause profound wide anion gap metabolic acidosis, and may be potentially lethal. After correction of circulation deficits, bicarbonate replacement alone may be sufficient in the treatment of acidosis, and there may be no need for haemodyalisis.

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