Acute Myocardial Injury in Association with Metformin Toxicity

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Abstract

Metformin is one of the most commonly used oral hypoglycemic agents in the treatment of type 2 diabetes mellitus. Toxicity related to accidental or intentional ingestion of metformin is well reported in the pediatric literature. We report a case of transient acute myocardial injury documented by biochemical and electrophysiological evidences in an adolescent male who presented with intentional ingestion of a large dose of metformin. To our knowledge, this is the first such case of documented reversible myocardial injury in relation to metformin toxicity to be reported in the pediatric literature.

Keywords

- metformin toxicity
- lactic acidosis
- myocardial injury

Case Report

A 17-year-old male with no significant past medical history presented to the emergency room shortly after ingestion of 20 tablets of metformin (total dose of 10,000 mg; 0.173 g/kg body weight) with suicidal ideation. He had ingested his grandmother's medication from the cabinet at home. He was not known to have prior suicidal attempts or psychiatric history and was not taking any long-term medications. On presentation, he had severe abdominal pain and emesis. The initial assessment revealed somnolence, with vital signs as follows: blood pressure 150/104 mm Hg, pulse 130/min, and respiratory rate 30/min. The rest of physical examination was documented as otherwise normal. The baseline laboratory findings were as follows: blood glucose level, 17 mg/dL; arterial blood gases: pH 7.045, pCO₂ 30.6, HCO₃ 8 mmol/L, and BE -21.3; creatinine 1.55 mg/dL; lactic acid 5.5 mmol/L; and anion gap of 43. The standard urine and serum drug screens, including for narcotics, were negative, and a 12-lead electrocardiogram (ECG) was normal (►Fig. 1). He was initially managed with intravenous isotonic saline, sodium bicarbonate, and dextrose bolus. The hypoglycemia was rapidly corrected after the dextrose bolus.

Given the severe metabolic acidosis and initial profound hypoglycemia, he was transferred to the pediatric intensive

care unit (PICU) for further management. Due to altered sensorium and combative behavior, he was sedated and intubated in the PICU. The calculated sequential organ failure assessment (SOFA) score upon admission to the PICU was 8, with a predicted hospital mortality rate of 15%. In spite of sodium bicarbonate infusion with the intravenous fluids, serial biochemistry findings showed persistence of high anion gap metabolic acidosis due to worsening lactic acidosis along with progressive renal dysfunction (►Fig. 2).

About 6 hours after arrival to the PICU, bedside telemetry was noted to show ST segment elevation and therefore a 12-lead ECG was performed. There was diffuse ST segment elevation of > 2 mm in most precordial and in the inferior limb leads (►Fig. 1). Due to this finding, cardiac enzymes (CPK-MB, troponin I) were assessed and were found to be elevated suggestive of myocardial injury (►Fig. 2). A transthoracic echocardiogram obtained at this time demonstrated a structurally normal heart with normal biventricular size and function. There were no regional wall motion abnormalities noted. There was no pericardial effusion. It was postulated that the myocardial injury was acute and resulting from the metabolic derangements secondary to metformin toxicity. Serial ECG and cardiac enzymes were obtained subsequently (►Fig. 2). The peak serum CPK-MB level reached 12.6 ng/mL (normal range: 0.0–6.7 ng/mL) on day 2.

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Fig. 1 Serial electrocardiograms during the hospitalization: baseline normal, day 1 showing diffuse ST segment elevation (arrows), day 3 normalization.

There were worsening metabolic acidosis and renal dysfunction (maximum creatinine of 2.18 mg/dL) which were not responding to conventional management. In addition, there was ECG evidence of myocardial injury. In view of these findings, hemodialysis was initiated approximately 12 hours after arrival to the PICU, to facilitate clearance of metformin and continued for approximately 3 hours. This was followed by continuous renal replacement therapy for an additional 30 hours. The patient had an adequate response to this treatment. There was progressive normalization of cardiac enzymes, and by day 3 of hospitalization, the ECG and the cardiac enzymes returned to normal, along with attainment of normal renal function and of lactate levels. Initial metformin level of 6.1 $\mu\text{g/mL}$, prior to hemo-

dialysis progressively trended downward by day 3 of management to 2.2 $\mu\text{g/mL}$. On day 4 of hospitalization, he was transferred to the inpatient psychiatric unit without any sequelae. He was diagnosed to have schizophreniform disorder and was subsequently treated with antipsychotic medications.

Discussion

Biguanides are a group of oral antidiabetic medications, which include metformin, phenformin, and buformin. Metformin is the most commonly used oral hypoglycemic agent in this group. It is considered first-line therapy for the treatment of type 2 diabetes mellitus across all age groups

Fig. 2 Laboratory trends after initiation of hemodialysis.

including children.¹ Due to its widespread availability in the medicine cabinets of many US households, it is one of the drugs with high potential for accidental as well as intentional ingestion in the pediatric age group. There have been a few reports of metformin-associated lactic acidosis (MALA) in the pediatric literature.^{2,3} Accidental ingestion is usually seen among toddlers, whereas intentional ingestion with suicidal ideation is observed commonly in the adolescent age group. The majority of the adverse effects of metformin are gastrointestinal in nature. Lactic acidosis is a serious but rare adverse effect associated with metformin use. MALA, a potentially lethal side effect of metformin, not only frequently presents in patients with predisposing factors, such as chronic kidney disease,^{4,5} but can also present in the context of acute ingestion in a previously healthy individual.^{5,6} In healthy individuals, MALA is often reported with overdose (>5,000 mg/dose). MALA is defined as lactic acidosis in a patient with metformin ingestion, in the absence of any other lactate-inducing mechanism, such as sepsis.⁷

Although its precise incidence is unknown, it is estimated to be around 0.03 to 0.06 per 1,000 patient-years,⁶ being more common in adult diabetic patients, and rare in the pediatric population.² The exact mechanism by which metformin induces lactic acidosis has not been fully elucidated.

This is the first reported case of myocardial injury in association with metformin toxicity in a previously healthy child. Metformin has been found to be safe when used in conventional doses in adult nondiabetic patients with ST segment elevation myocardial infarction.⁸ Our patient presented with deliberate metformin overdose, which resulted in MALA and acute kidney injury. There was also ST segment elevation along with increase in cardiac Troponin I levels indicative of myocardial injury. The management aimed at rapidly reducing the severe lactic acidosis (>24 mmol/L) and removal of metformin in this patient, resulted in rapid improvement and subsequent normalization of the cardiac enzymes and 12-lead ECG. This suggests that the myocardial injury in this condition is rapidly reversible without potential long-term sequelae with appropriate management of the toxicity.

The authors' literature search did not reveal any cases of metformin overdose-related acute myocardial injury in the pediatric population. However, White et al⁹ reported a case of an adult diabetic patient with lactic acidosis presenting as acute myocardial infarction with ST elevation and elevated cardiac enzymes. That case differed from ours in that there was no drug overdose, but rather a worsening of renal function resulting in accumulation of metformin. Additionally, the patient also had electrolyte imbalances that could have potentially explained her initial ECG findings (i.e., hyperkalemia). Nevertheless, there are various clinical findings from our case that mirror the case reported by White et al. In both cases, the echocardiogram did not portray an altered cardiac function. Additionally, complete normalization of ECG findings and cardiac enzymes was seen after hemodialysis. Moreover, there was also a complete recovery of renal function, as well as normalization in lactate levels. These latter findings are also in agreement with previously reported cases of lactic acidosis in the context of metformin overdose, in which there was a complete resolution after initiation of hemodialysis.^{3,7,10,11}

Although there is limited evidence of myocardial injury in the context of metformin intoxication, we hypothesize that there may be poorly understood mechanisms that may link lactic acidosis and myocardial injury which need to be further elucidated and studied. This is presumptive, given the strong temporal correlation of lactate and metformin levels with cardiac troponin I levels and ECG findings.

Conclusions

Metformin associated lactic acidosis is a rare but potentially fatal side effect of metformin overdose. Consequently, it is important to be aware of this condition and its management. Additionally, it is important to conduct more research about its pharmacology, given that there are aspects of this condition that are not fully understood. Moreover, given the low

incidence of MALA, this case report provides additional evidence about its adequate response to hemodialysis without any sequelae. Furthermore, it opens up a new clinical aspect of MALA that has not been described before, that of myocardial injury.

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Conflict of Interest

None.

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