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Severe Metformin poisoning; Experience at a tertiary care hospital in Sri Lanka: a case series

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Abstract

Metformin is the first line medication used for the treatment of type 2 diabetes mellitus worldwide. It has been considered a cost effective and safe drug for decades. Though, lactic acidosis is a recognized adverse effect of metformin, it is sparsely seen with therapeutic doses. However, it occurs frequently in patients with metformin overdose and in the presence of renal insufficiency. Metformin associated lactic acidosis (MALA) carries a mortality rate of almost 50%. Early initiation of renal replacement therapy has shown to reduce morbidity and mortality in these patients. Metformin overdose is relatively uncommon and only few cases of severe metformin overdose are reported in the literature. Here, we discuss five cases of MALA due to severe metformin poisoning. Four of them were successfully treated with early use of renal replacement therapy.

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Introduction

Metformin is a biguanide, used in the management of diabetes mellitus. It reduces plasma glucose by several mechanisms: reducing gluconeogenesis, reducing glycogenolysis, increasing peripheral uptake of glucose, enhancing intestinal glucose consumption and decreasing fatty acid oxidation (1, 2, 3. 4, 5). Metformin is available only in oral form and it reaches its peak plasma concentration within 2 hours of ingestion. The drug is excreted via kidneys unmodified. In acute metformin overdose, the toxic effects occur due to accumulation of metformin as a result of the saturation of clearance mechanisms of the kidney. (1,6)

The toxic dose of metformin is yet to be established and it is found that the metformin levels do not correlate well with clinical presentations. However, evidence indicates that higher levels are associated with dire complications such as severe lactic acidosis, cardiovascular compromise, and renal insufficiency. Other clinical presentations include nausea, vomiting, abdominal pain, myalgia and altered mental status. Hypoglycaemia and less commonly hyperglycaemia have also been reported in patients with acute metformin overdose. (7,8,9,10)

MALA is a well-recognized, potentially fatal, rare adverse effect that is reported in acute overdose (11,12,13). MALA has also been described in patients with acute on chronic metformin toxicity, end stage renal disease and in patients with acute renal failure on chronic metformin therapy (13,14). Its incidence varies from 3 to 10 per 100 000 patients (11,14,15,16). Metformin increases lactic

acid production by reducing hepatic gluconeogenesis. In addition, it suppresses the lactate metabolism in the liver, inhibits mitochondrial respiration and also exerts a negative inotropic action on the heart, all of which lead to lactatemia (17,18,19). Development of acidemia may take 6 to 24 hours and severe acidemia can lead to altered mental status, coma, hypotension, and respiratory insufficiency and it is often associated with acute kidney injury (20,21).

Here we discuss five patients who presented with severe Metformin poisoning who were managed in a tertiary care hospital in Sri Lanka.

Case 1

A 16-year-old, previously well, schoolgirl, was transferred from the local hospital to the Toxicology Unit, Teaching Hospital Peradeniya for management of metformin overdose. She had self-ingested a month's supply of her grandmother's medication (about 120 of 500 mg tablets) with suicidal intent. Decontamination with gastric lavage and activated charcoal was done at the local hospital. On admission, i.e.,6 hours after drug ingestion, she was asymptomatic except for mild epigastric discomfort, and she was haemodynamically stable. However, her initial arterial blood gas showed severe metabolic acidosis with a pH value of 7.08, pCO2 of 20 mmHg, pO2 of 158 mmHg, HCO3 of 5.9 mmol/L, base excess of -22 mmol/L and a lactate value of 13 mmol/L. Plasma glucose remained high between 200-300 mg/dL in the first twenty-four hours. The patient was admitted to the toxicology high dependency unit (HDU) for close monitoring. She was started on a sodium bicarbonate 100 mmol /hour infusion together with symptomatic treatment until hemodialysis (HD) took place. At the 12th hour of ingestion of metformin, haemodialysis with bicarbonate containing dialysate was initiated. However, she could not tolerate HD due to haemodynamic instability despite adequate fluids and vasopressors. HD had to be discontinued and continuous renal replacement therapy (CRRT) remained the only option. As there was a delay setting up CRRT due to limited availability, she was maintained on a sodium bicarbonate infusion and inotropes. Patient remained conscious and systolic blood pressure was maintained at 100 mmHg with a noradrenalin 0.5 mcg/kg/hour infusion. Around the 14th hour into ingestion, the patient's haemodynamic condition started to deteriorate further. She became drowsy due to further drop of blood pressure and the second vasopressor had to be started. Her metabolic acidosis worsened with a pH of 6.8, HCO3 of 3 mmol/L and base excess of -30 mmol/L. Lactate levels were persistently more than 15mmol/L. Patient was electively intubated. CRRT was only started at the 20th hour of metformin ingestion when she was barely maintaining a mean arterial pressure (MAP) of 65 mmHg with maximum doses of noradrenaline, adrenalin, dobutamine and vasopressin. After 72 hours of CRRT, her haemodynamic parameters improved transiently together with biochemical and blood gas parameters. However, she developed features of sepsis with disseminated intravascular coagulation (DIC), acute kidney injury and liver failure. At the same time, it was noted that her pupils were unequal, raising the possibility of intracranial haemorrhage. CT brain could not be performed as the patient was not haemodynamically stable to be mobilised. Despite supportive treatment, the patient succumbed to death on day 8 of metformin overdose due to multiorgan failure.

Case 2

A 70-year-old man was admitted to hospital with an altered level of consciousness. He had vomited twice on the way to the hospital and had no other symptoms. His past medical history was uneventful. He was not on any long term medication or narcotics. On admission he was maintaining his airway and respiratory system examination was normal. His pulse rate was 100 beats per minute and blood pressure was 80/50 mmHg. His Glasgow Coma Scale (GCS) was 12/15 with normal reactive pupils. There were no focal neurological signs or other evidence to suggest a convulsion or head injury. His random plasma glucose was 138 mg/dL and the temperature was

normal. Initial fluid bolus was followed by normal saline and noradrenaline infusions. His initial venous blood gas showed metabolic acidosis with a pH of 7.18, HCO3 of 9.7 mmol/L, and base excess of -18 mmol/L. Lactate level was more than 15mmol/L. The patient developed repeated episodes of hypoglycaemia, worsening metabolic acidosis and the lactate levels remained more than 15 mmol/L. Serum electrolytes including sodium, potassium, calcium and magnesium concentrations, sepsis screening and other toxin screens were normal. Computer tomography of the brain was normal. Hence the possibility of metformin overdose was suspected, and hemodialysis with bicarbonate containing dialysate was commenced. The patient improved after 4 hours of HD and his conscious level, hemodynamic parameters and the lactic acidosis further improved after a few more sessions. Once fully conscious, the patient admitted to having ingested a handful of Metformin tablets with suicidal intent. During the hospital stay, he developed acute kidney injury needing regular hemodialysis. After a hospital stay of 18 days with hemodialysis every other day, the patient made a complete recovery and was discharged on a nephrology and psychiatry follow up plan.

Case 3

A 17-year-old schoolgirl presented after 12 hours following self-ingestion of 40 tablets of 500mg metformin. She complained of vomiting and generalised abdominal pain on admission. Her past medical history was unremarkable. She was haemodynamically stable and her GCS was 15/15. Her random plasma glucose was 200 mg/dL. However, her initial venous blood gas showed severe metabolic acidosis with a pH of 7.17, HCO3 of 7.3 mmol/L, base excess of -19 mmol/L and a lactate level greater than 15 mmol/L. She was commenced on a 100 mmol per hour sodium bicarbonate infusion till urgent hemodialysis with bicarbonate containing dialysate was arranged. Her lactic acidosis rapidly improved after the first dialysis and no further dialysis was needed. She was discharged on the 5th day of hospital stay without any complications.

Case 4

A 17-year-old girl was transferred to the toxicology unit, TH Peradeniya, after ingestion of 50 tablets of 500mg Metformin 24 hours back. She had vomited several times and had complained of dizziness and difficulty in breathing at the local hospital. On admission to our hospital, she was hypotensive, tachycardic and had a GCS of 10/15. She was started on a noradrenaline infusion after fluid resuscitation. Arterial blood gas revealed severe lactic acidosis with a pH of 6.8, HCO3 of 3.2 mmol/L, base excess of -22 mmol/L and lactate greater than 15 mmol/L. She was started on a sodium bicarbonate infusion and admitted to the intensive care unit (ICU) for CRRT. After 48 hours of CRRT her blood gas was normalised. Patient was discharged on day 10 of admission after complete recovery with a follow up plan at a psychiatry clinic.

Case 5

An 18-year-old girl admitted to the toxicology unit, TH Peradeniya after 3 hours following ingestion of 100 tablets of 500 mg Metformin. She was conscious and haemodynamically stable. Gastrointestinal decontamination with gastric lavage and activated charcoal was carried out to reduce absorption of metformin and she was monitored in the HDU. Initial arterial blood gas showed a pH of 7.32, HCO3 of 12mmol/L and base excess of -16 mmol/L with lactate of 10 mmol/L. She was started on high dose insulin euglycemic therapy (HIET) with soluble insulin 0.5U/kg infusion and dextrose infusion titrated to maintain sugar levels in the range of 140-180mg/dL. Serum potassium was monitored 2 hourly and corrected accordingly. Blood gas repeated after 3 hours showed worsening metabolic acidosis with a pH of 7.17 and HCO3 of 8 mmol/L. Hence it was decided to arrange hemodialysis. In the interim a sodium bicarbonate infusion was commenced. While waiting for dialysis, the patient gradually became restless and confused. Her blood pressure crashed requiring two inotropes for maintenance. The patient was

transferred to ICU and CRRT was initiated after 9 hours following the ingestion of metformin. HIET was continued in addition to other supportive treatments. After 24 hours of CRRT, the patient showed improvement in lactic acidosis and haemodynamic parameters. Intubation was not required for this patient. After 3 days of CRRT and HIET, she was deescalated from ICU care to ward care. HD sessions were continued till she recovered from acute kidney injury. The patient was discharged 11 days following admission.

Discussion

Overdose with metformin is rare and its clinical presentations are highly nonspecific. Without a clear history of overdose, clinicians should have a high index of suspicion to diagnose the condition. Toxicity can cause severe consequences including death, mainly due to metformin associated lactic acidosis (MALA). Hence, Metformin ingestion should always be considered in the differential diagnoses of any patient with metabolic acidosis and high lactate level. (22,23).

In this case series, we discussed 4 females (aged 16-18 years) and a male (70 years) who presented with a massive Metformin overdose. The minimum number of tablets taken was 40 while maximum was 120. The duration from ingestion to hospital admission varied between 3-24 hours. Two were hypotensive on admission while another two developed hypotension later. Their arterial blood gases showed pH varying from 6.8-7.32, bicarbonate varying between 3-12 mmol/L with severe high anion gap metabolic acidosis. All patients had evidence of severe lactic acidosis (10-15 mmol/L) regardless of the time duration from ingestion of metformin to admission (Table 1). Except the male patient who had repeated hypoglycemia, others had normal or high blood sugar levels.

There is no specific antidote for metformin toxicity. The mainstay of treatment is supportive care to maintain the fluid status, acid base balance, electrolytes, and cardiovascular stability together with enhanced elimination of the toxin (24,25). All five patients were managed with maximum supportive care. Fluid resuscitation and infusion of inotropes/vasopressors were used to maintain the circulation.

Activated charcoal should be considered in patients who present soon after ingestion, provided that there are no contraindications (10, 26). Two patients received GI decontamination. Sodium bicarbonate may be considered in severely acidotic patients who are not responding to supportive measures, as acidosis can impair cardiovascular function and increase mortality. However, the benefits of bicarbonate in metformin toxicity is unclear (10, 11, 24, 27). It may be reasonable to initiate bicarbonate as a buffer until hemodialysis is initiated. All 5 patients were started on intravenous fluid resuscitation and vasopressors according to clinical parameters. All the patients were started on sodium bicarbonate bolus doses and continuous infusions initially due to severe acidosis. However, it was evident that sodium bicarbonate infusion has only a minimal or no benefit, because the clinical condition of all the patients deteriorated despite this treatment eventually needing hemodialysis. But it may delay the clinical deterioration of the patient by controlling the acidosis till hemodialysis is available. Hence in low-income countries like Sri Lanka, where hemodialysis facilities are not readily available, sodium bicarbonate infusion may be used as an initial bridging therapy.

Metformin can effectively be dialysed owing to its properties such as high-water solubility, minimal protein binding and small molecular weight. Hence it has been used successfully in patients with MALA due to chronic overdose or acute overdose. Some general recommendations for initiating dialysis are: 1) lactate concentration greater than 20 mmol/L 2) pH less than or equal to 7.0 3) presence of shock 4) decreased level of consciousness and 5) failure to respond to standard supportive care (22, 18, 28). Main aims would be to correct the acid base disturbance and to remove metformin from the body. The treatment could be performed with conventional hemodialysis (HD) or continuous renal replacement therapy (CRRT) and the latter is more

Table 1 - Summary of cases

Age (years)	Gender	No. of Tablets ingested	Time from ingestion to admission	Premorbid condition	symptoms	On admission BP	On admission GCS	ABG*				Gastric decontamination	Therapy	Progression & Outcome
								pH	HCO_3	BE	Lactate			
16	F	120	6 H	NAD	Mild epigastric pain	Stable	15	6.8	3	-30	>15	Yes	HD** CRRT**	An episode of hyperglycaemia Intubated Inotropes AKI/ALI MOF →died
70	M	A handful	unknown	NAD	Drowsiness Vomiting	Low BP	12	7.18	9.7	-12	>15	No	HD	Recurrent hypoglycaemic episodes AKI D18 discharged
17	F	40	12 H	NAD	Abdominal pain Vomiting	Stable	15	7.17	7.3	-19	>15	No	HD	D5 discharged
17	F	50	24 H	NAD	Vomiting Difficulty in breathing	Low BP	10	6.8	3.2	-22	>15	No	CRRT	D10 Discharged
18	F	100	3 H	NAD	Asymptomatic	Stable	15	7.32	12	-16	10	Yes	HIET HD CRRT	AKI D11 discharged

F- Female, **M**- Male, **H**- hours, **BE**- Base excess, **BP**- Blood Pressure, **HD**- Haemodialysis, **CRRT**- Continuous Renal Replacement Therapy, **HIET**- High dose insulin euglycaemic therapy, **AKI**- Acute kidney injury, **ALI**- Acute lung injury, **MOF**- Multi organ failure, **ABG**- Arterial blood gas, **NAD**- Nothing abnormal detected

*ABG values corresponding to the most critical stage of the patient are included

**From the time of admission, there was a 12 H delay in arranging HD while CRRT took place 20 H later

suitable for haemodynamically unstable patients (24, 25, 29). Use of bicarbonate dialysate may increase metformin clearance (22, 17, 27). In intentional acute poisoning, early dialysis is likely to be more beneficial as it will prevent the drug being redistributed into the tissues. This is because metformin has a large volume of distribution, and also it has been suggested that prolonged dialysis may be needed to see a beneficial effect (30, 31, 32). All five patients with severe metformin poisoning needed hemodialysis and showed clinical response only following the procedure. Hence, early initiation of hemodialysis in severe metformin poisoning is likely to aid in reducing the morbidity and mortality of these patients.

High dose insulin dextrose therapy or hyperinsulinemic euglycemic therapy which is a standard treatment of beta blocker and calcium channel blocker toxicity, has been shown to be effective in metformin toxicity as well. This therapy includes providing a high dose of insulin together with dextrose in order to prevent hypoglycaemia. Insulin facilitates glucose utilisation, sustains glycolysis, attenuates lipolysis and enhances lactate utilisation in the myocardium as an energy source. High dose insulin also increases cardiac output without increasing myocardial oxygen demand. A few clinical studies have shown a significant mortality benefit in patients who were treated with insulin dextrose when compared to those that were not (24, 33, 34). We initiated insulin dextrose infusion on admission on one of the patients with severe metformin poisoning. However, the patient continued to deteriorate despite the insulin dextrose therapy and bicarbonate infusions, needing hemodialysis.

Few case studies report that methylene blue may be beneficial in metformin toxicity as methylene blue could help to bypass the electron transport impediment at mitochondrial level seen in these patients (3, 35, 36). In addition, it has shown to be effective in reducing the metformin induced vasodilatory effects and improving haemodynamics. Evidence for its use and an appropriate regime is still inadequate, however it may be used as an option for treatment in patients with severe acidosis and distributive shock who are poorly responding to vasoactive agents (35). We did not use this treatment method in our patients due to lack of evidence on its use.

Conclusion

Metformin toxicity is a serious clinical condition associated with severe lactic acidosis and significant mortality. Recommendations for effective therapies are limited. The mainstay of treatment includes gastrointestinal decontamination, supportive care with fluids and vasopressors and early initiation of hemodialysis. Further clinical studies using a larger number of patients will be beneficial to improve the clinical management of these patients.

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