Metabolic Acidosis and Rhabdomyolysis with Metformin Overdosage

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Metformin is a biguanide oral hypoglycemic agent used as first-line or as a part of multi-drug therapy in the treatment of Type 2 Diabetes Mellitus (DM). Lactic acidosis is a well-known but relatively uncommon adverse effect of Metformin, especially in patients with co-existing renal failure. There are several case reports of inadvertent or intentional Metformin overdosage resulting in severe metabolic acidosis with hyperlactatemia and often fatal outcome. Continuous hemodiafiltration with other supportive therapies have resulted in successful management of the metabolic derangements and is presently the accepted standard therapy of Metformin intoxication.

A twenty-two-year-old female presented with Metformin over-dosage of 50g and developed severe metabolic acidosis and rhabdomyolysis. Metabolic acidosis was prolonged; the pH level was 6.72, bicarbonate level <4 mmol/L and lactate level was more than 25 mmol/L. The patient was managed with crystalloids, bicarbonate infusions and continuous venovenous hemodiafiltration. The blood gas parameters normalized 48 hours after initiation of the treatment. Hemodiafiltration was continued for longer than usual due to the prolonged metabolic acidosis and until the elevated Creatine Kinase (CK) levels returned to normal. She made an uneventful recovery, without residual sequelae.

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Metformin is a biguanide oral hypoglycemic agent used as first-line or as a part of multi-drug therapy in the treatment of Type 2 Diabetes Mellitus. It exerts its action by increasing insulin sensitivity of target organs and decreasing hepatic glucose production[1]. Lactic acidosis is a well-known but relatively uncommon adverse effect of Metformin, especially in patients with coexisting renal failure[2-4]. There are several case reports of inadvertent or intentional Metformin overdosage resulting in severe metabolic acidosis with hyperlactatemia and often with a fatal outcome[5-14].

The aim of this report is to highlight a well-known but relatively uncommon adverse effect of lactic acidosis following Metformin overdosage.

THE CASE

We present a case of a 22-year-old female, with no history of medical or psychiatric illness. She had allegedly consumed 50g of Metformin 6 hours before presentation. The patient presented in a state of altered sensorium, was able to localize noxious stimuli, but there was no lateralizing neurologic signs. The blood pressure was normal, she had mild tachycardia, the respiratory rate was more than 30/minute and was normothermic. Chest, cardiac and abdominal examinations were unremarkable.

Initial blood gas analysis revealed severe high anion gap metabolic acidosis with partial respiratory compensation and significantly raised lactate levels. PH level was 7.202, bicarbonate was 10 mmol/L, anion gap was 22 and lactate level was 10.47 mmol/L. Subsequent blood gas analysis revealed worsening metabolic acidosis with pH level of 6.72, bicarbonate of 4.4 mmol/L and lactate level of up to 25.16. Blood glucose was low at presentation, for which, she received 50% dextrose water. There were no further episodes of hypoglycemia. White blood cell count was mildly increased at admission and continued to rise 24 hours post-admission; however, there were no clinical signs of infection and CRP level was not significantly raised. Serial tests of renal and liver functions and coagulation parameters were within acceptable limits. Creatine Kinase level was high at presentation and continued to rise 24 hours after admission.

Elective endotracheal intubation was performed and mechanical ventilation was initiated. Hourly blood gas analysis in the ICU showed worsening metabolic acidosis and increasing anion-gap and lactate levels, despite intravenous boluses of crystalloids and bicarbonate infusion. Continuous venovenous hemodiafiltration was initiated 2 hours after admission to treat the metabolic acidosis and to accelerate the clearance of Metformin and lactate. There was a marked improvement in the blood gas parameters; pH and bicarbonate levels returned to normal about 48 hours after admission. Renal Replacement Therapy was continued as the CK levels were high and was discontinued after 72 hours. Table 1 shows the chronological details of blood gas and relevant laboratory parameters.

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Table 1: Laboratory Parameters

		0h	1h	2h	4h	6h	9h	12h	18h	24h	30h	36h	48h	60h	72h	96h
pH		7.202	7.018	7.000	6.728	7.117	6.998	7.094	7.159	7.148	7.260	7.374	7.367	7.413	7.443	7.459
HCO3	mmol/L	10.7	5.0	4.9	4.4	14.3	7.5	8.6	9.8	9.8	13.6	19.2	21.0	28.2	22.7	20.6
PCO2	mmHg	28	19.5	20.4	24	45	31.1	28.6	28.2	28.9	30.9	33.6	37.5	45.2	34	29.7
BD	mmol/L	17.3	26.0	26.4	31.3	15.1	23.8	21.2	18.9	19.1	13.5	6.1	4.3	-3.6	1.4	3.2
Lactate	mmol/L	10.47	12.78	16.83	20.81	18.12	23.82	24.78	25.16	17.28	9.51	4.21	1.94	1.41	1.28	0.94
AG	mmol/L	22.2	39	32.5	37.8		39.6	42.2	43.6	35.8	26.7	15.0	12.5	6.9	11.0	9.9
K^+	mmol/L	2.98	3.49	4.12	3.65	5.01	3.38	4.26	4.3	4.79	4.35	4.0	3.79	3.84	3.4	4.15
Glucose	mmol/dL	7.5	12.5	11.4	15.2	13.1	5.5	14.2	17.3	7.7	12.7	9.3	9.2	9.1	7.4	7.2
Creatinine	mmol/L	127.6								126.03			71.05		40.4	
CK	U/L	339.4		978.9		2551		3429		3610	3547	3126	3240	2237	1453	
ALT	U/L	32.64								64.64			73.2		87.88	
WBC	1.10^3/cu.mm	12.05				26.49				41.81			18.3		6.46	
CRP	mg/L	1.2								1.5			41.1		40.4	

The patient regained full consciousness within hours after initiation of Continuous Renal Replacement Therapy (CRRT), but was kept well-sedated for comfort and mechanical ventilation. She was weaned off mechanical ventilation and endotracheal tube 48 hours post-admission. CRRT was discontinued 72 hours after admission. She was transferred to the normal wards 96 hours after admission. She was subsequently discharged from the hospital in a perfectly normal state after a psychiatric evaluation.

DISCUSSION

High anion-gap metabolic acidosis with hyperlactatemia is a well-known but rare adverse effect of Metformin therapy; the reported incidence varies between 6-40 per 100,000 patient/years; higher incidence reported with increasing severity of coexisting renal impairment[1-15]. Although not fully understood, uncoupling of oxidative phosphorylation by inhibition of Complex1 of the mitochondrial electron transport chain is postulated to be responsible for the severe metabolic acidosis seen with Metformin toxicity[1,16].

Metformin is excreted largely unchanged in the urine with a serum half-life of 1.5 to 6 hours. Therefore, preexisting severe renal or hepatic impairment or intentional overdosage are the primary etiologies of Metformin toxicity. There are several reports, both adult and pediatric, of intentional Metformin overdosage, ranging from a few grams up to 100 grams[11-14].

Clinical symptoms of Metformin intoxication are vague and non-specific, such as abdominal pain, nausea, vomiting and acute confusional state. Hypotension, lactic acidosis, hypoglycemia, hypothermia, acute renal failure, coma, pancreatitis and cardiac arrest are clinical features of more severe intoxication[14]. Mitochondrial toxicity, ATP depletion and anaerobic metabolism in the absence of hypoxemia are thought to be responsible for the severity of the acidosis and multi-organ dysfunction[15].

The overall mortality rate from Metformin-associated lactic acidosis is 30%-50%; it is higher in patients with significant preexisting illnesses, particularly renal or hepatic impairment and other drugs that cause lactic acidosis[17,18]. There is no definite correlation between blood lactate levels, pH, serum Metformin levels and mortality[17,18]. Lactate level as high as 40 mmol/L, pH as low as 6.59 and bicarbonate levels as low as <2 mmol/L have been reported in survivors of Metformin overdosage[18]. Our patient had a low pH of 6.72 and a peak lactate level of 25.16 mmol/L. Metformin level has been suggested to have no diagnostic or prognostic value in these cases. Blood lactate level has been suggested as a surrogate monitoring tool[19]. We monitored our patient with serial blood gas analysis and blood lactate level.

Rhabdomyolysis in Metformin overdosage has only been reported in patients who co-ingested Metformin with other drugs or in patients with concomitant trauma or compartment syndrome[20,21]. Our patient had prolonged and markedly elevated CK levels after ingestion of Metformin alone.

The management of Metformin toxicity includes volume expansion, bicarbonate infusions and continuous or intermittent hemofiltration with bicarbonate buffer[22-35]. In our patient, the acidosis was prolonged and blood lactate level normalized 48 hours after admission and continuous hemodiafiltration. Additionally, rhabdomyolysis and markedly elevated CK levels required longer periods of hemodiafiltration. Intermittent hemodialysis, as well as Slow Low-Efficiency Hemodialysis (SLED), have been used successfully for the treatment of Metformin toxicity. Cases treated with continuous or intermittent hemofiltration have a significantly reduced mortality risk, and those without any premorbid illnesses have survived without any sequelae[27-37].

Methyl Succinate may be an intervention for Metformin toxicity in the future. It has been found to bypass the Complex1 inhibition and restore ATP production in isolated cell experiments[38-40].

CONCLUSION

Early initiation of continuous venovenous hemofiltration may lead to a successful outcome of Metformin overdosage. Longer periods of hemofiltration may be warranted in cases with refractory lactic acidosis. Rhabdomyolysis may be seen with Metformin intoxication, but further research is needed before a definite correlation could be made.

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