Case Report

Metformin Poisoning : Lactic Acidosis

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ABSTRACT

Metformin is an oral antihyperglycemic agent widely used in the management of Type 2 diabetes mellitus. Lactic acidosis from metformin overdose is a rare complication of metformin therapy and occurs infrequently with therapeutic use. Fatal cases, both accidental and intentional, are extremely rare in clinical practice. Metformin is eliminated by the kidneys, and impaired renal function can result in an increased plasma concentration of the drug. We report the case of lactic acidosis following intentional suicidal intake of 20 grams of metformin in a patient with diabetes. The patient had a baseline Creatinine Clearance of 35ml/min, resulting in severe acidosis with a nadir pH of 7 associated with circulatory collapse. She was successfully treated with intravenous soda bicarbonate and intermittent hemodialysis.

Case Report :

A 63 year old female, with a weight of 70 Kg and height of 165 cm, was brought by relatives to Emergency Medical Service with complaints of ingestion of 40 tablets of metformin 500 mg (Total = 20 gm). Patient was a known case of Type 2 Diabetes Mellitus and Hypertension for the past 15 years and was on regular medications. Patient presented after 5 hour of ingestion and was admitted in Medicine ICU.

On admission, patient was conscious oriented and afebrile with a Pulse rate of 82/min, Respiratory rate of 20/min and Blood Pressure of 90/60 mmHg. Systemic examination was not suggestive of any obvious abnormality. ECG Suggestive of normal sinus rhythm. Blood was drawn for investigation and had baseline serum creatinine of 1.3mg/dl. Patient was given a Ryle's tube lavage. Her blood sugar was 660 gm/dl with negative Urine Ketones, with no tachypnea or acidotic breathing. She was given an insulin infusion for her hyperglycaemia. Over next 6 hrs. patient had a Urine output of less than 200ml she became drowsy and developed acidotic breathing and her BP decreased to 80/62. Her abdomen was tender but no guarding or rigidity was observed. Repeat Serum Creatinine was 1.8 mg/dl with potassium of 5.7 mEq/lit. Arterial blood Gas analysis was suggestive of High anion gap Metabolic acidosis ***(Table 1).*** Serum lactate was 14 mmol/lit. Patient also developed uncontrolled hyperglycaemia which was managed by continuous intravenous insulin infusion along with intravenous fluids and vasopressor support to keep MAP above 65 and was started on Inj. SodaBicarbonate correction. Patient was planned for urgent Hemodialysis (HD). After one session of 3 hours HD, patients was still in shock and ABG still showed Severe High anion gap metabolic acidosis. Repeat Serum Creatinine of 2 mg/dl with a urine output of less than 400 ml in last 24 hours. On third day of Ingestion, patient was again given of 4 hour session of HD with flow rate of 300 ml/hour. Patient was continued on inotrope support to maintain MAP of 65. Few hours after 2nd HD session, ABG showed improvement with a pH = 7.47, PCO2 = 19, HCO3 = 13.8, Lactate of 10.9. Patient's blood pressure thereafter stabilised, her urine output progressively increased and her Inotropes were tapered. Ultrasonographic study was s/o bilateral grade 1 Renal Parenchymal disease with increased echotexture and Urine Protein of 3+. Over next two days, the lactates normalized with level of 0.9 mmol/lit, HCO3 levels improved, she was off inotropes with BP of 110/70, adequate Urine output and starting taking orally.

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Table 1 : **Serial ABG Reports**

	12 hrs. after ingestion	6 hrs. after 2nd session of 4 hours Haemodialysis	24 hrs. after 2nd session of 4hr Haemodialysis
pH	7.1	7.47	7.48
Lactate (mmol/lit)	14	10.9	0.9
Bicarbonate (mol/lit)	3.7	13.8	19.4
PCO2 (mmHg)	12	19	26
Sodium (mol/lit)	143	139	143
Chloride (mol/lit)	103	98.6	99.8

Discussion :

Metformin is widely used and is the most frequently prescribed oral antidiabetic drug of the biguanide family. Metformin inhibits hepatic gluconeogenesis and glycogenolysis and enhances peripheral glucose utilisation in patients with non-insulin-dependent diabetes. Metformin use is generally safe and well tolerated. However, lactic acidosis is a well-known complication of metformin, especially in intentional overdose or in cases of renal insufficiency. Metformin poisoning is a life-threatening condition with a very high mortality rate.

Severe metformin poisoning often presents with a profound lactic acidosis followed by collapse of the cardiovascular system. Symptoms of metformin poisoning are diffuse with abdominal pain, nausea, vomiting, decreased level of consciousness, and circulatory instability leading to multiorgan failure. The circulatory instability is due to peripheral vasculoplegia as described in many case reports where low systemic vascular resistance was measured.

Treatment of metformin poisoning is symptomatic and supportive. Typical treatment strategies consist of correcting acidosis with intravenous sodium bicarbonate and decreasing the blood levels of metformin. In case of renal insufficiency, renal replacement therapy is the only option for metformin removal and acidosis correction. Metformin is readily dialyzable. It is a small molecule with a molecular weight of 165 Da, not protein bound, and after gastrointestinal absorption it rapidly moves into the tissue compartment and has a large volume of distribution of 63276 L (15 L/kg). *Lalau et al.* previously demonstrated a biphasic pattern of metformin elimination according to a two-compartment model. This two-compartment model suggests that a brief hemodialysis session is not sufficient in eliminating metformin due to a rebound phenomenon. These pharmacokinetic properties indicate a need of prolonged dialysis for metformin elimination. Several case reports describe favourable outcome after severe metformin poisoning treated with prolonged intermittent HD. Substitution with bicarbonate in case of lactic acidosis is controversial as there are concerns that treatment with bicarbonate can increase intracellular acidosis. However, bicarbonate treatment is widely used to stabilise metabolic acidosis in cases of metformin poisoning as described in the literature. We used high doses of bicarbonate as intravenous infusion and highest possible concentration of bicarbonate buffer in the HD machine simultaneously. We observed worsening of the acidosis and cardiovascular status after 1st HD session and we presume this deterioration to be due to lack of bicarbonate buffer. Renal replacement therapy, including conventional HD and CVVH, offers both theoretical and practical advantages over bicarbonate infusion. These allow for isovolemic correction of the metabolic acidosis while removing metformin and lactate. Recent recommendations for metformin poisoning from the Extracorporeal Treatments in Poisoning Workgroup advocate for intermittent HD, but continuous renal replacement therapies may be considered if HD is unavailable. Initiation of dialysis is suggested in very severe cases, when lactate concentration is > 15 mmol/L and pH < 7.0 together with shock or organ failure. In our opinion, these recommendations are more applicable in situations of metformin-

associated lactic acidosis, as in acute high dose metformin poisoning the acidosis accelerates very fast and the patient's condition deteriorates dramatically with development of circulatory collapse. We therefore suggest that in cases of acute high dose metformin poisoning HD should be initiated earlier than that stated in the recommendations.

Our patient also had profound and progressive hyperglycemia. Metformin generally does not cause significant alterations in serum glucose levels, even in overdose situations. Unlike the sulfonylurea and meglitinide classes of diabetes drugs, which stimulate insulin release from the pancreas and therefore lower the glucose level, the biguanide drugs have more complex effects on glucose homeostasis that tend to reduce hyperglycemia without inducing hypoglycemia.

Hyperglycemia has been related to acute pancreatitis in a few cases of metformin toxicity from both intentional overdose and therapeutic dosing. The potential mechanism for the severe hyperglycemia in our patient is not clear. Nothing among metformin's known mechanisms would logically explain the progressive and severe hyperglycemia, especially since these mechanisms should tend to limit the glucose level. However, if one considers what might occur if the patient could no longer secrete enough insulin, as may occur with pancreatitis, then a potential explanation arises. It is also possible that a counter-regulatory hormone surge (epinephrine ± glucagon) from the acute physiologic stress of the overdose contributed to the hyperglycemia. Nevertheless, pancreatitis remains a promising potential mechanism, as our patient's clinical presentation with complaints of vomiting and abdominal pain is consistent with previously reported cases of metformin-associated pancreatitis and serum lipase was also raised 3 times in this case.

Conclusion :

Metformin induced Lactic Acidosis (MALA) is rare condition found in a severe overdose often in underlying decreased renal function. Metformin toxicity often leads to severe Metabolic acidosis with circulatory collapse, requiring Vasopressor support and acidosis correction. Repeated Hemodialysis is frequently required to correct lactic acidosis and also to clear toxic levels metformin from plasma, even when Patient is on vasopressor for maintaining Mean Arterial Blood pressures above 65. So, even severe Metformin toxicity can be treated with timely intervention like Intravenous bicarbonate correction, Hemodialysis and inotropes support for cardio-depression till acidosis is corrected.

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