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CASE REPORT

Metformin Overdose and Severe Lactic Acidosis

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ABSTRACT

Metformin belongs to biguanide group of oral hypoglycemic drugs which is used in combination with other oral hypoglycemic agents in patients suffering from type II diabetes mellitus. It is used with caution in patients with renal impairment and liver dysfunction as it is excreted through renal and hepatic routes. Metformin toxicity may be intentional or accidental and although the actual toxic mechanism remains unclear, it is usually associated with severe lactic acidosis. This case report is about a young female who intentionally ingested 30g of metformin, and focuses on presentation, emergency resuscitative measures, investigations, and definite management plan.

This case was reported to show that the Metformintoxicity is usually not reported and that if we institute early dialysis and reverse the high anion gap acidosis, the chances of survival can significantly improve.

KEY WORDS

Metformin toxicity, lactic acidosis, hemodialysis

INTRODUCTION

Metformin is the principal biguanide in clinical use. Lactic acidosis is known to be the major toxicity of acute or chronic biguanide use.1 Though lactic acidosis remains to be the main presentation of metformin toxicity, however when used in combination with other agents its toxicity can present with hypoglycemia as well.2 Metformin associated lactic acidosis is commonly seen in patients with underlying kidney or liver disease but is also observed in cases of acute ingestion.3 This case describes a scenario in which a young lady overdosed with metformin, landed in emergency department with severe lactic acidosis and was successfully managed with hemodialysis and other supportive measures.

CASE SUMMARY

A young female, 18 years old, with previously known anxiety disorder on relaxants (10 mg escitalopram once daily) presented to the emergency department with complains of shortness of breath, nausea, multiple episodes of vomiting, abdominal pain, and generalized body weakness. There was no history of fever, cough, or chest pain. On further inquiry patient gave history of ingestion of 30 tablets of metformin/sitagliptin (1000mg+2.5mg) making it a total dose of 30 grams of metformin and 75 milligrams of sitagliptin, a day before presentation to the hospital. Patient was initially taken to another hospital where her gastric lavage was done, and she was sent home after being kept under observation for a couple of hours. Next morning, she developed an episode of hypoglycemia (27mg/dl) at home which was treated with home remedies.

On presentation in our department, she had following vitals: blood pressure: 145/75 mmHg, Heart rate: 122 bpm, respiratory rate: 26/min, was afebrile, maintaining oxygen saturations of 94% at room air and her GCS was 15/15. There was no significant finding on her systemic examination. Initially her random blood sugars were 463mg/dL whereas her venous blood gases showed pH of 6.895, bicarbonate of 6.6 mmol/l, potassium 5.57 with anion gap of 29.43. ECG had normal sinus rhythm. Further investigations revealed serum lactate of >120mmol/l, creatinine of 2.23 mg/dl, BUN of 14mg/dl, blood ketones were negative. Liver function tests, serum amylase, lipase and Creatinine Phosphokinase were all with in normal limits. Total leukocyte count was 35,700/dL, whereas urinary toxicology screen which included amphetamines, barbiturates, cannabinoids, opiates and benzodiazepines were all negative. Patient was initially resuscitated with intravenous fluids, a liter of normal saline bolus, along with 50 mEq of sodium bicarbonate. Nephrology was taken on board, 4-hour hemodialysis was done in emergency room. Her repeat blood gas showed pH of

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7.25 and bicarbonate of 20.7mmol/l. Patient was admitted in critical care unit where she was managed conservatively with maintenance fluids, her blood sugars were monitored periodically. Psychiatric input was taken as well. Her serial blood gases are mentioned below.
practices of emergency medical services and care.

Table 1. Lab Measurements

Sr. Number	Ph	Hco3	Pco2	Lactate
1.	6.89	5.7	30.2	>120
2.	7.25	20.7	48.0	-
3.	7.35	20.5	37.3	5.7
4.	7.41	21.1	33.8	1.9

Patient improved clinically, her lab workup showed improving trend of creatinine from 2.23 mg/dl to 0.95 mg/dl and downward trend of leukocyte count to 14,600. She was discharged in stable condition on 3rd day of admission with follow up in psychiatric and nephrology clinics.

DISCUSSION

Oral bioavailability of metformin is 50-60% which decreases with increased dose.[2] It is dialyzable with half-life of 4-9 hours, acts by decreasing gluconeogenesis and alimentary canal absorption of glucose and by increasing target cell sensitivity to insulin.[2,3] Mechanism of metformin associated lactic acidosis is complex. It promotes the conversion of glucose to lactate in the splanchnic bed of small intestine, decreases hepatic gluconeogenesis from lactate, pyruvate and alanine which results in additional lactate and substrate for lactate production.[1,3,4]

Due to limitations of data available on metformin toxicity, the exact toxic dose of metformin remains unknown hence any patient presenting with intentional ingestion of metformin especially with underlying systemic disease such as renal impairment, liver disease or heart failure, or children ingesting one or more tablet, should be suspected for metformin toxicity.[1]

Toxicity as high as 90 grams with successful outcome has been described in literature.[2]

Metformin associated lactic acidosis is associated with high mortality rate (50-60%), and very rare (1:30,000), a case series showed that 5 out of 6 patients with pH below 6.9 and lactate above 25 mmol/l did not survive.[5,6,7]

Lactic acidosis itself is known for high mortality and results when pH is lower than 7.25 and lactate in the serum is higher than 5 mmol/l. Two types of lactic acidosis are recognized: type A and type B where B is further classified into three groups.[8,9,10]

Type A: Triggered by hypoxia, which may result from tissue hypoperfusion in cases of left ventricle failure, reduced cardiac debit, asphyxia, hypoxemia, severe anemia or carbon monoxide poisoning.

Type B 1: In cases of sepsis, acute renal failure, hepatic disease, diabetes mellitus, neoplasms, malaria, cholera

Type B 2: Resulting from drug toxicity (biguanides-metformin, fenformin and others like aspirin, isoniaside, catecholamines, paracetamol, sodium nitroprusside, etc).

Type B 3: In the cases of increased physical activity, grand-mal seizures, etc.

Usually the patients presenting with metformin toxicity are not fit for hemodialysis but in this case a young otherwise physically healthy patient had ingested 30 gram of metformin and had serum lactate levels of greater than 120 mmol/l, therefore prompt dialysis, intravenous bicarbonate and aggressive fluid resuscitation led to a positive outcome. Her acidosis had led to a raised leukocyte count and blood sugars secondary to insulin resistance and sympathetic overdrive, hence were not aggressively managed rather monitored continuously and normalized once acidosis settled.

Sitagliptin, a partially dialyzable drug, with dose clearance of 13.5 % after 3-4 hours of hemodialysis has some noticeable side effects including nasopharyngitis, pancreatitis, diarrhea, headache, nausea, and constipation some of which were observed in this case. Prompt initialization of dialysis not only led to the clearance of metformin but also sitagliptin leading to a better outcome and early resolution of her symptoms.

CONCLUSION

Metformin overdose is not frequently reported. Different case series suggest that urgent dialysis and aggressive resuscitation is the key to management and if initiated early, can lead to survival of patients even with severely low pH or raised serum lactate levels.

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