Management of Sitagliptin and Metformin Combination Toxic Overdose

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Abstract

Metformin and Sitagliptin are often used in combination in the management of non-insulin dependent diabetes mellitus. Though toxicity is rare, but occurs more frequently in cases of intentional or unintentional overdose of these drugs. Here, we present a case of an intentional overdose of a metformin-sitagliptin combination (70g metformin and 3500mg sitagliptin) in a suicide attempt by a young non-diabetic female who presented with severe lactic acidosis and was successfully treated with prompt hemodialysis and bicarbonate therapy.

Introduction

Metformin, an oral anti-diabetic agent of biguanide class is a first line drug used for treatment of non-insulin dependent diabetes mellitus (NIDDM) mainly for its potent insulin sensitizing action. Its adverse event profile essentially manifests in the form of common gastrointestinal symptoms such as nausea, vomiting, gastritis and abdominal pain. Lactic acidosis, is a rare, but fatal adverse effect of metformin, with a reported incidence of about three per 100,000 person-years, and a reported mortality of up to 50%. Sitagliptin, another oral anti-diabetic agent, is a DPP-4 Inhibitor (Di Peptidyl Peptidase- 4) agent which acts on the incretin axis, and is used either as an add-on therapy to metformin or as monotherapy in patients intolerant to metformin or in combination with both oral agents as well as insulin. These drugs are essentially well tolerated and are not known to cause hypoglycemia, and are rapidly gaining acceptance for use in NIDDM. A combination of Sitagliptin and Metformin is commonly prescribed owing to these safety aspects as well as better and sustained HbA1c reduction compared to monotherapy with either drug alone. Though a number of cases of overdose with either metformin alone or sitagliptin alone have been reported in the past, we report a case of a suicidal attempt by a non-diabetic person with an overdose of combination pills of sitagliptin and metformin who presented our hospital with severe metformin associated lactic acidosis (MALA) and recovered well after successful treatment with hemodialysis and sodium bicarbonate.

Case Report

A 37 year old non-diabetic lady was admitted to our hospital after an overdose of 70 fixed-dose combination pills containing Sitagliptin 50 mg + Metformin 1000 mg each, amounting to a total ingestion of 3500 mg of sitagliptin and 70,000 mg (70 g) of metformin in a suicidal attempt. She had been suffering from depression and was under psychiatric treatment and on and off for the same since the past 6 months. She herself was a non-diabetic and the pills had been prescribed to her husband who had type 2 diabetes. She had a history of hypothyroidism which was adequately controlled on thyroxine 100 mcg daily.

She developed vomiting within half an hour of ingestion of the pills which eventually got worse. Once she started getting abdomen discomfort and loose motions, the family attributed it to eating out and home remedy was given. 4-5 hours later when the abdominal discomfort got worse, she disclosed about the intentional overdose and was rushed to her family physician who treated her with iv dextrose anticipating hypoglycemia and sent her home. Her condition deteriorated about 8 hours after ingestion and she was then brought to our hospital in a very restless and agitated state with excruciating pain in her legs.

She was lethargic and irritable, and responding to verbal commands with a GCS score of 13/15. Her pulse was 80/min and BP was 90 mm Hg systolic. Random blood glucose levels was 263 mg/dl and temperature was 98 degrees F. She was admitted to the ICU and gastric lavage was done.

Her ABG revealed severe metabolic acidosis with a pH of 6.89, serum bicarbonate 3 and a serum lactate >15 mmol/l. Urine ketones were absent and a diagnosis of metformin associated lactic acidosis secondary to intentional overdose of sitagliptin and metformin was made. Her blood urea nitrogen at admission was 10.6 mg/dl with a serum creatinine of 1.8 mg/dl and a serum potassium level of 4.3 mEq/l. Her HbA1c was 4.6%, haemoglobin was 14.2 gm% with a total leucocyte count 17900/cumm and a total platelet count of 2.6 lacs/mm⁴. Prothrombin time and INR were raised respectively at 27.9 sec and 2.11. Serum amylase, lipase, lactate dehydrogenase as well as CPK were normal. She was given 50 ml sodium bicarbonate intravenously and ABG was monitored 4-hourly based on which a total 270 ml of sodium bicarbonate was administered over 10 hours.

An immediate nephrology consult was done and she was started on Slow Low Efficiency Dialysis (SLED) to correct severe metabolic acidosis at a blood flow rate of 200 ml/hour which was continued over 8 hours. This removed the lactate as well as metformin and sitagliptin out of circulation. She maintained an adequate urine output all through her hospitalization.

She had partially recovered in 12...
hours with a pH of 7.2 and was drowsy though arousable. Her leg pain had considerably reduced. She gradually improved with dialysis as the lactate was cleared from her system and her arterial blood pH normalized as shown in Table 1. A slight but gradual drop was seen in her total platelet counts although her PT and INR were normalized. Her TLC showed a transient rise which was normalized within 48 hours. By 24 hours she was fully conscious with a pH of 7.4. She eventually recovered well and was shifted out of the ICU on the fourth day, psychiatry opinion was taken and she was discharged in a stable state from hospital by the 5th day.

Discussion

The highest reported case for metformin overdose alone was 90 gm² and that for sitagliptin alone was 1700mg.³ Hence, to the best of our knowledge ours is the only reported case of an overdose of both the drugs together at doses of metformin 70 gm and sitagliptin 3500 mg as well as probably the first reported case of a patient surviving after such an overdose. Though we did not have the expertise to measure her plasma sitagliptin or metformin concentration, we did have the empty strip packs as evidence of the massive overdose which was recovered from her room by her family after her hospitalization.

An overdose of metformin generally does not induce dysglycemia, though a few cases of hypoglycemia (probably due to concomitant overdose of an oral hypoglycemic agent such as a sulphonylurea) as well as hyperglycemia (induced probably due to severe toxicity caused by an overdose or pancreatitis) have been reported.

Metformin associated lactic acidosis (MALA) is the most feared and potentially fatal adverse effect of metformin with a high mortality rate. Metformin in toxic doses affects the electron transport chain in the mitochondria causing an inhibition of oxidative metabolism. Anaerobic metabolism takes over and eventually causes an elevation in lactate levels leading to lactic acidosis.

In our case involving consumption of 70 g of metformin, immediate correction of acidosis as well as clearance of lactate by hemodialysis and sodium bicarbonate resulted in rapid recovery. The severity of acidosis in this case could be a compound effect of not only MALA but also acidosis induced by hypotension as well as acute renal failure. Hemodialysis not only corrects acidosis by removing lactate but also removes metformin, thus reducing further lactate production.⁴ Also, sufficient correction of her volume depletion, adequate potassium replacement as well as maintenance of a good urine output contributed to a speedy recovery besides the fact that this patient was relatively young without any associated chronic comorbidities.

Another noticeable occurrence in our patient was a transient rise in PT/INR as well as a transient fall in Hb, which gradually normalized on its own as the patient stabilized. We attributed this transient hemolysis to be another rare side effect of metformin overdose.⁵ Her hyperglycemia at admission was attributed to increased insulin resistance secondary to acidosis as well as glycogenolysis due to sympathetic overactivity as part of the body’s stress response, and normalized on its own without insulin once she was stabilized and acidosis was corrected. The transient leucocytosis at admission was also secondary to acidosis and catecholamine release and normalized on its own.

The adverse effect profile of sitagliptin as well as other DPP-4 inhibitors includes concerns regarding pancreatitis, renal impairment, hypersensitivity reactions such as angioedema, anaphylaxis, exfoliative skin manifestations, nasopharyngitis and upper respiratory tract infections, headache and peripheral edema. A small increase in white cell count, predominantly neutrophilia has been documented, though it is clinically irrelevant. Very rarely myalgia, arthralgia, lower extremity pain and back pain have also been reported in a few cases.

In our case, even after consumption of 35 times the recommended dose, our patient did not really develop any of the feared adverse events that could be directly attributed to sitagliptin per se. She did present with severe lower extremity pain as well as a transient leucocytosis, which could be an effect of the severe acidosis as well. A controlled clinical study in healthy people with 800 mg dose of sitagliptin showed a mean increase of 8.0 msec in QTc which was not considered clinically important.⁶ In our case, even with a much higher dose, no significant changes were observed in the patient’s electrocardiogram.

The fact that she did not develop any hypoglycemia vouches for the safety of Sitagliptin as an anti-hyperglycemic drug that has purely a glucose-dependent action both in diabetics as well as non-diabetics. Sitagliptin, being a moderately dialyzable drug, has shown 13.5 % dose clearance over a 3-4 hour hemodialysis session in clinical safety studies of this drug.⁷ Hence, early and sustained hemodialysis helped in clearing both these drugs from our patient’s system aiding in her speedy recovery.

Conclusion

Prompt institution of measures to curb the systemic effects of lactic acidosis can ensure a favorable outcome in an as-yet unreported clinical scenario like ours, where the toxic dose ingested was 70 grams of Metformin and 3.5 gram Sitagliptin.

References