

Renal Replacement Therapy for Metformin and Sitagliptin Overdose

Ahmad Chaaban¹, Nicole Gebran², Ali El Houni³, Khuloud Alamri¹, Bassam Bernieh¹

Departments of ¹Nephrology, ²Pharmacy and ³Endocrinology, Tawam Hospital, A Ain, Abu Dhabi, United Arab Emirates

Abstract

Metformin and sitagliptin are widely used in the management of type 2 diabetes mellitus. We present a case who reported ingestion of an overdose of metformin and sitagliptin in a suicidal attempt. The patient presented with severe lactic acidosis, hypotension, and hyperglycemic acute kidney injury, successfully treated medically with intravenous infusion of fluids and sodium bicarbonate, and prompt convection hemodialysis.

Keywords: Diabetes, dialysis, metformin, overdose, sitagliptin

INTRODUCTION

Metformin is a biguanide typically used as a first-line drug in the treatment of type 2 diabetes mellitus (T2DM). It reduces absorption of glucose from the gastrointestinal tract, decreases hepatic gluconeogenesis, and increases peripheral utilization of glucose.^[1] Its adverse effects are mainly in the form of gastrointestinal symptoms of nausea, vomiting and abdominal pain, and lactic acidosis which carries a high mortality rate.^[2] Sitagliptin is a member of the incretin-based drugs, a class of oral hypoglycemic agents for the management of diabetes that elevate the plasma concentration of active glucagon-like peptide-1 through inhibition of dipeptidyl peptidase-4 (DPP-4). They effectively lower not only glycosylated hemoglobin levels but also fasting and postprandial plasma glucose levels.^[3] These two medications are commonly used in combination. They are well tolerated and not known to cause hypoglycemia. Accidental overdose is extremely rare.

We present a case of deliberate metformin and sitagliptin overdose in a suicidal attempt in which patient presented with lactic acidosis and hyperglycemia.

CASE REPORT

A 57-year-old male presented to the Emergency Department complaining of abdominal pain, vomiting, and tachypnea. He reported ingestion of more than 25 g metformin and 2.5 g sitagliptin in a suicidal attempt. The patient had a history of

T2DM and normal baseline kidney function. On examination, he was hypotensive (blood pressure: 90/60 mmHg) and tachypneic. His initial laboratory studies showed high serum creatinine 191 mmol/L, serum potassium 5.9, serum lactic acid 13.6 mmol/L (later increased to 21.9 mmol/L), plasma pH 7.19, and plasma CO₂ 9 with a high anion gap of 38. He also has a random plasma glucose of 18 mmol/L and mild elevation in the liver and pancreatic enzymes. The patient was immediately started on IV sodium bicarbonate and urgent hemodialysis. Within 24 h, the patient had full recovery of his severe lactic acidosis, renal impairment, and liver derangement.

DISCUSSION

Metformin is generally used as an antidiabetic medication with a very good safety profile when used by the professional recommendations. Data from a Cochrane Review in 2010 indicate no cases of fatal or nonfatal lactic acidosis in 70,490 patient years of metformin use.^[4] Type B lactic acidosis related to metformin use occurs mostly among patients with renal insufficiency.^[4] Suicidal attempts using metformin and sitagliptin is a rare incident perhaps due to the profile of patients to whom they are prescribed, size of the tablets,

Address for correspondence: Dr. Nicole Gebran,
Department of Pharmacy, Tawam Hospital, PO Box 15258, Al-Ain,
Abu Dhabi, United Arab Emirates.
E-mail: ngebran@seha.ae

Access this article online

Quick Response Code:



Website:
www.ijmbs.org

DOI:
10.4103/ijmbs.ijmbs_72_17

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Chaaban A, Gebran N, El Houni A, Alamri K, Bernieh B. Renal replacement therapy for metformin and sitagliptin overdose. *Ibnosina J Med Biomed Sci* 2018;10:68-70.

and lack of any established public stereotypic perception for them as suicidal drugs. Nonetheless, a few cases have been reported in the literature.^[5,6] Clinically, patients with metformin overdose may present with varying degrees of lactic acidosis with signs and symptoms appearing as a result of the acidosis. These features may include coma as well as tachypnea, hyperpnea, tachycardia, and severe acidosis that may often lead to hypotension. Decreased catecholamine binding to their receptors at low pH causes vasodilation. Decreased myocardial contractility which contributes to hypotension and hypoperfusion may lead to acute kidney injury and multiorgan failure.^[5,6]

Metformin-induced lactic acidosis is not well understood and not well correlated to the clinical picture. Metformin in toxic doses affected electron transport chain in the mitochondria causing inhibition of oxidative metabolism; anaerobic metabolism takes over eventually elevating lactic acid levels leading to lactic acidosis.^[7-10]

Treatment of metformin overdose includes gastrointestinal decontamination and metformin adsorbs well to activated charcoal.^[11,12] Intravenous volume loading with crystalloid and vasopressor support may be required for hypotension. Correction of acidosis with sodium bicarbonate remains controversial.^[13] Lactate and metformin can be readily removed from the circulation by intermittent hemodialysis while continuous venovenous hemofiltration is considered superior to intermittent hemodialysis concerning the hemodynamic stability.^[14] Whenever possible, a prolonged session of hemodialysis should be undertaken. Continuous renal replacement therapy may alternatively be considered. The patient was fortunate enough with prompt access to acute renal services in the hospital. If he was initially admitted elsewhere, lack of such facility and the delay necessitated by transfer could have affected the outcome adversely.

A noteworthy event in our patient was the occurrence of hyperglycemia with overdose of two oral antidiabetic agents! Hyperglycemia could be attributed to an increased insulin resistance secondary to the lactic acidosis as well as glycogenolysis due to sympathetic overactivity as part of the body's stress response in addition to pancreatitis.^[15,16] The recognized adverse effects of sitagliptin as other DDP4 inhibitors include concerns regarding pancreatitis, renal impairment, and hypersensitivity. A single oral overdose of sitagliptin was not shown to cause hypoglycemia or any other adverse effects. Sitagliptin being a moderately dialyzable drug has shown 13.5% dose clearance over 3–4 h of a hemodialysis session.^[15,16]

A limitation of this report is that serum levels of metformin and sitagliptin were not documented. However, severity of the overdose could be inferred by the ingested amounts in comparison with the maximal daily dose ($\times 12.5$ for metformin and $\times 25$ for sitagliptin).

The relative contribution of the two drugs cannot be ascertained because of the overlap between the clinical side

effect profiles of the two drugs. Nonetheless, metformin seems to be culprit in the induction of lactic acidosis, with sitagliptin playing a secondary role in worsening the GI side effects and enhancing the precipitation of the acute kidney injury. An isolated sitagliptin overdose in an 86-year-old woman with T2DM and depression was reported previously.^[17] She was transferred to the emergency room 4 h after ingestion of 1700 mg of sitagliptin. On arrival, she was fully conscious, plasma glucose was 124 mg/dL, and serum immunoreactive insulin level was 5.81 μ U/mL. Although the plasma concentration of sitagliptin rose to 3793 nM (4.5 times higher than the value found under regular treatment with the maximum dose), the patient did not suffer from hypoglycemia nor any of the other features seen in the present case report. Further support to this notion comes from a retrospective review of isolated gliptin-exposure cases reported to a state poison control system in 2006–2012.^[18] The majority of gliptin-exposed adult and pediatric/adolescent patients were reportedly safely managed at home and, when evaluated in a health-care facility, did not require hospitalization. Intentional self-harm-adult gliptin exposures were managed in a health-care facility but rarely resulted in hospitalization or serious morbidity at doses up to 18 times the adult therapeutic dose.

CONCLUSIONS

Deliberate overdose with metformin is rare but should not be treated with any degree of complacency. It may result in serious consequences such as elevated lactic acid which seems to have a different outcome from other types of lactic acidosis. Our findings and those of others indicate that early initiation of renal replacement therapy is very successful in managing this critical condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authors' contributions

All authors contributed to the care of the patient, drafting of the case report, revision, and approval of its final version.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is required for single case reports. However, the patient provided consent for publication as stated above.

REFERENCES

1. Douglas Pharmaceutical Ltd. Glucomet. Metformin Hydrochloride 500 mg and 850 mg Tablets; Douglas Pharmaceutical Ltd.; 1999. Available from: <http://www.medsafe.gov/profs/datasheet/glucometab.htm>. [Last accessed on 2017 Jun 27].
2. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 1998;21:1659-63.
3. Duez H, Cariou B, Staels B. DPP-4 inhibitors in the treatment of type 2 diabetes. *Biochem Pharmacol* 2012;83:823-32.
4. Lalau JD. Lactic acidosis induced by metformin: Incidence, management and prevention. *Drug Saf* 2010;33:727-40.
5. Wills BK, Bryant SM, Buckley P, Seo B. Can acute overdose of metformin lead to lactic acidosis? *Am J Emerg Med* 2010;28:857-61.
6. Bosse GM. Antidiabetic and hypoglycemic agents. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland M, Hoffman RS, Nelson LS, editors. *Goldfrank's Toxicologic Emergencies*. 7th ed. New York: McGraw-Hill; 2002. p. 593-605.
7. Kruse JA. Review: Metformin does not increase risk for lactic acidosis or increase lactate levels in type 2 diabetes. *ACP J Club* 2004;141:7.
8. Ahmad S, Beckett M. Recovery from pH 6.38: Lactic acidosis complicated by hypothermia. *Emerg Med J* 2002;19:169-71.
9. Dell'Aglia DM, Perino LJ, Todino JD, Algren DA, Morgan BW. Metformin overdose with a resultant serum pH of 6.59: Survival without sequelae. *J Emerg Med* 2010;39:e77-80.
10. Agterhuis D, Freling H, Henstra M, Veneman TF. Metformin Intoxication: A Case of a Combination of Severe Hypoglycaemia and Severe Lactic Acidosis (LA). *J Diabetes Mellitus* 5:111-4. <http://dx.doi.org/10.4236/jdm.2015.52013>
11. Yang PW, Lin KH, Lo SH, Wang LM, Lin HD. Successful treatment of severe lactic acidosis caused by a suicide attempt with a metformin overdose. *Kaohsiung J Med Sci* 2009;25:93-7.
12. Chang CT, Chen YC, Fang JT, Huang CC. High anion gap metabolic acidosis in suicide: Don't forget metformin intoxication – Two patients' experiences. *Ren Fail* 2002;24:671-5.
13. Spiller HA. Management of antidiabetic medications in overdose. *Drug Saf* 1998;19:411-24.
14. Rifkin SI, McFarren C, Juvvadi R, Weinstein SS. Prolonged hemodialysis for severe metformin intoxication. *Ren Fail* 2011;33:459-61.
15. Kopec KT, Kowalski MJ. Metformin-associated lactic acidosis (MALA): Case files of the Einstein medical center medical toxicology fellowship. *J Med Toxicol* 2013;9:61-6.
16. Sehra S, Jaggi S, Sehra D, Aggarwal R, Saraswat V, Juneja D, *et al.* Management of sitagliptin and metformin combination toxic overdose. *J Assoc Physicians India* 2016;64:80-1.
17. Furukawa S, Kumagi T, Miyake T, Ueda T, Niiya T, Nishino K, *et al.* Suicide attempt by an overdose of sitagliptin, an oral hypoglycemic agent: A case report and a review of the literature. *Endocr J* 2012;59:329-33.
18. Darracq MA, Toy JM, Chen T, Mo C, Cantrell FL. A retrospective review of isolated gliptin-exposure cases reported to a state poison control system. *Clin Toxicol (Phila)* 2014;52:226-30.

Reviewers:

Abdulfattah Lakhdar (London, UK)
Lisbet Brandt (Copenhagen, Denmark)

Editors:

Salem A Beshyah (Abu Dhabi, UAE)
Elmahdi Elkhammas (Columbus, Ohio, USA)