Case Report

Extracorporeal treatment with high-volume continuous venovenous hemodiafiltration and charcoal-based sorbent hemoperfusion for severe metformin-associated lactic acidosis

Suneel Kumar Garg, Omender Singh, Desh Deepak, Akhilesh Singh, Rohit Yadav, Kirti Vashist

Abstract

We present a case of a 49-year-old female with an alleged history of ingestion of approximately 100 tablets of metformin (850 mg each). Investigations revealed severe lactic acidosis with lactate levels of 13.5 mmol/L and pH of 7.17. This indicates severe toxicity and is associated with a high mortality. Charcoal-based sorbent hemoperfusion was done as a desperate effort, as patient continued to deteriorate despite supportive care and high-volume continuous venovenous hemodiafiltration. The patient survived despite metformin-associated lactic acidosis related to severe metformin toxicity.

Keywords: Charcoal hemoperfusion, extracorporeal, metformin

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.182205

Quick Response Code:

Introduction

Metformin is a biguanide antihyperglycemic agent commonly used as a glucose-lowering agent for the treatment of type-II diabetes mellitus and is considered safe. The potentially life-threatening complication of metformin overdose is metabolic acidosis described as metformin-associated lactic acidosis (MALA). There are only limited descriptions of metformin overdose in the literature. Early recognition, correction of metabolic acidosis, intensive support of the cardiovascular system, and maintenance of body temperature and drug removal, mainly by extracorporeal therapy, are the essential aspects of management as metformin is dialyzable. Patients who are treated with high-volume continuous venovenous hemodiafiltration (CVVHDF) have a better outcome. As per the American Association of Poison Centre (2004), only few patients (0.05%) needed extracorporeal treatment for poisoning.[1] Extracorporeal treatment, particularly charcoal-based, may be lifesaving in patients with clinical evidence of severe toxicity such as lactic acidosis, shock, and hypoglycemia in patients who are not responding to supportive management.

Case Report

A 49-year-old female, known case of type-II diabetes mellitus (on insulin), portal hypertension, and rheumatic heart disease, was admitted with an alleged history of consumption of 100 tablets of metformin (850 mg each, total dose 85 g) around 2 h prior to presentation. She presented with nausea, vomiting, and shortness of breath. On admission, she was conscious, heart rate was

From:
Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi, India

Correspondence:
Dr. Suneel Kumar Garg, Institute of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi - 110 017, India.
E-mail: dr_garg@hotmail.com

How to cite this article: Garg SK, Singh O, Deepak D, Singh A, Yadav R, Vashist K. Extracorporeal treatment with high-volume continuous venovenous hemodiafiltration and charcoal-based sorbent hemoperfusion for severe metformin-associated lactic acidosis. Indian J Crit Care Med 2016;20:295-8.

88/min, blood pressure was 80/40 mmHg, respiratory rate was 28/min, and was afebrile. Her random blood sugar was 88 mg% on admission. Her arterial blood gas revealed severe metabolic acidosis with hyperlactatemia (pH 7.17 with lactate of 13.5 mmol/l). She was intubated electively, and appropriate fluid resuscitation was done. In view of persistent hypotension, she was started on vasopressors. Gastric lavage was done with 100 g of activated charcoal in emergency room. She was shifted to Intensive Care Unit for further management. She was continued on vasopressors and started on 50% dextrose and 7.5% sodium bicarbonate infusions. She developed repeated episodes of hypoglycemia despite 50% dextrose infusion, and hence, glucagon bolus 2 mg followed by 1–2 mg/h infusion to target blood sugar level >100 mg% was initiated. She was also started on high-flow CVVHDF. Hyperlactatemia gradually worsened with increasing levels (13.5, 15, 22, 24, and 27 mmol/l) over 8 h [Chart 1]. In view of refractory hypoglycemia and refractory metabolic acidosis, charcoal-based sorbent hemoperfusion was started as rescue therapy [Figure 1] and high-volume CVVHDF was continued.

The patient's condition started improving with increase in mean arterial blood pressure and decreasing lactate [Chart 1] around 6 h after starting charcoal-based sorbent hemoperfusion. Another session of charcoal-based sorbent hemoperfusion was given after 12 h. Hypoglycemia and lactate levels gradually improved over the next 24 h. Vasopressors, 50% dextrose, glucagon, and sodium bicarbonate were progressively weaned off in the next 48 h and stopped on day 3. CVVHDF without charcoal hemoperfusion was continued for the next 72 h and stopped after that as shock resolved, and acid–base status became normal [Chart 1]. The patient was extubated on day 4 and discharged on day 6 in stable condition with psychological consultation and counseling.

Chart 1: Serial arterial blood gas

Date and time	pH	PCO_2	PO_2	HCO_3	Lactate
February 11, 2015, 03.07 am	7.172	36.2	94.6	12.8	13.5
February 11, 2015, 04.26 am	7.109	38	107	10.9	15
February 11, 2015, 06.13 am	7.069	26.5	111	7.3	22
February 11, 2015, 09.50 am	7.056	17.5	209	4.7	24
February 11, 2015, 10.38 am	6.971	21.4	203	4.7	27
February 11, 2015, 12.14 pm	6.939	25.9	158	5.3	25
February 11, 2015, 03.08 pm	7.153	28.3	132	9.5	21
February 11, 2015, 05.17 pm	7.117	31.1	134	9.6	20
February 11, 2015, 07.20 pm	7.231	38.9	138	15.7	13.5
February 11, 2015, 10.11 pm	7.302	37	143	17.8	10.6
February 12, 2015, 01.16 am	7.308	40.3	112	19.6	8.9
February 12, 2015, 04.13 am	7.369	36.2	106	20.4	8.3
February 12, 2015, 08.34 am	7.392	39.9	128	23.7	5.6
February 12, 2015, 12.52 pm	7.465	33.5	143	23.7	4.3
February 12, 2015, 05.52 pm	7.501	28.4	134	22	2.2
February 12, 2015, 11.21 pm	7.538	30.2	118	25.6	2.3
February 13, 2015, 04.03 am	7.487	36.3	89.1	27.1	1.7
February 13, 2015, 03.18 pm	7.441	35.3	90.6	23.6	1.4
February 13, 2015, 07.31 pm	7.477	37.7	141	27.5	1.8
February 13, 2015, 10.34 pm	7.454	41.7	71.5	28.8	1.9
February 14, 2015, 04.16 am	7.448	39.8	113	27.1	1.0
February 14, 2015, 08.49 pm	7.491	35.4	64.1	26.8	1.6
February 15, 2015, 04.50 am	7.514	37.5	90.8	30	1.1
February 15, 2015, 09.15 pm	7.471	37.1	73.6	26.7	1.5
February 16, 2015, 04.33 am	7.519	40	62	32.4	1.1

Discussion

Metformin is an antihyperglycemic agent of biguanide class used for the treatment of type-II diabetes mellitus. Metformin has a low bioavailability and takes a long time (around 6 h) to get completely absorbed from gastrointestinal tract. There are case reports of fatal intoxication with metformin with varying dosage, i.e., 60 g,[2] 76.5 g,[3] and 100 g.[4,5] In our case, the patient had consumed 85 g. Metformin decreases blood glucose in diabetic patients, causes weight loss, improves lipid profile, and also causes a reduction in blood pressure.[6]

Patients with metformin overdose usually present with abdominal pain, nausea, and vomiting. Hypoglycemia is rarely reported with biguanide exposure.[7] MALA is a life-threatening complication of metformin, which occurs either in cases of therapeutic dose or overdose or with concomitant risk factors, i.e., renal failure, liver and cardiovascular diseases, infection and alcoholics, and has a high mortality rate.[8] Metformin intoxication is known to cause acute renal failure, which aggravates toxicity.[9] With lactic acidosis, patients usually present with tachypnea, lethargy, hypotension, tachycardia, and shock,[10] if not treated in time, death is unavoidable. The estimated rate of MALA from previous studies is believed to range somehow between 4 and 9 cases per 100,000 patient-years.[11] Serum lactate levels do not

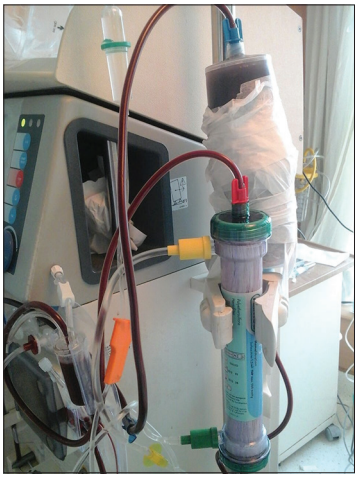

Figure 1: Extracorporeal therapy with continuous venovenous hemodiafiltration and charcoal-based sorbent hemoperfusion

correlate with prognosis. The pathogenesis of MALA is complex and not completely understood.[12] In our case also, the patient presented with nausea, vomiting, hypotension, and severe lactic acidosis.

Management of metformin toxicity is supportive and includes gastrointestinal decontamination, correction of acid–base abnormalities, hypoglycemia, and hemodialysis.[6] There is no specific antidote for metformin overdose. Hemodialysis should be performed in cases of lactic acidosis or impaired renal function.[13,14]

Success of hemodialysis depends on characteristics of the toxin, i.e., lipid solubility, molecular weight, volume of distribution, protein binding, and technique used for hemodialysis.[15] Metformin has a low volume of distribution, molecular weight of 166 Da, and has almost negligible plasma protein binding, hence hemodialysis is an effective modality for removal of metformin.[10]

In this patient, gastric lavage, activated charcoal, and other supportive care were given, and CVVHDF was initiated in view of shock and persistent lactic acidosis. In spite of CVVHDF, the patient had persistent shock, hyperlactatemia, and hypoglycemia and hence, charcoal-based sorbent hemoperfusion was incorporated along with CVVHDF. Till date, there is no report of using combination therapy with hemodiafiltration and hemoperfusion in metformin toxicity in the literature searched.

Despite their efficacy, the use of hemoperfusion cartridges has declined over the past 20 years, due to limitations of their indications and shelf life. To be removed by hemoperfusion, the toxic substance must have binding affinity to the sorbent in the cartridge and a low volume of distribution.

We used this modality as metformin meets all the characteristics required for efficient removal by charcoal sorbent. We continued CVVHD along with charcoal hemoperfusion because hemoperfusion lacks the efficacy of correcting acid–base, fluid, and electrolyte abnormalities.[16] The patient's condition started improving around 6 h after starting charcoal-based sorbent hemoperfusion. We also gave another session of charcoal-based sorbent hemoperfusion with CVVHDF after 12 h. Shock, hyperlactatemia, and hypoglycemia gradually improved and the patient weaned from the ventilator and extubated on day 4. The patient was discharged on day 6 in stable condition.

Conclusion

Metformin seems to cause more hypoglycemia than reported in literature and may be an important sign of severe toxicity. Although lactic acidosis associated with severe metformin toxicity can result in high morbidity and mortality, most of them may not require aggressive treatment including hemodialysis.

Acute metformin overdose is potentially life-threatening condition, and patients may have rapid clinical deterioration and death, if not treated in a timely manner. Patients with metformin toxicity and MALA should be treated aggressively with supportive measures and hemodialysis. Given the high mortality rate, patients who have refractory hyperlactatemia, refractory shock, and refractory hypoglycemia even with best supportive care and hemodialysis should be subjected to CVVHDF with charcoal-based sorbent hemoperfusion. Charcoal-based sorbent hemoperfusion may be lifesaving in such clinical scenario.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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