International Journal of Diabetes: Current Research
IJDCR, 2(1): 51-54
www.scitcentral.com
ISSN: 2644-3031
Case Study: Open Access

Combined Metformin-Associated Lactic Acidosis and Starvation Ketoacidosis with High Osmolal Gap

Ahmad Kofahi*, Mohammad Abu Hishmeh, Alina Wasim, Mohammad Aldiabat, Khaled Alabdallah, Jose Amaya-Suarez, Syed Haider Ali Shah, Donya Bani Hani and Shekar Murthy

Department of Internal Medicine, Lincoln Medical Center, Bronx, NY, USA.

Received March 26, 2020; Revised June 10, 2020; Accepted August 05, 2020

ABSTRACT

Metformin is mainly used in the control Type II Diabetes Mellitus. Metformin-Associated Lactic Acidosis (MALA) is a rare side effect of metformin that is primarily seen in patients with renal impairment. Only few cases of coexisting MALA and ketoacidosis have been reported, as case reports typically attribute high anion gap (AG) and osmolal gap (OG) to MALA and uremia. A case was reported with a 49-year-old man with type 2 DM and hyperlipidemia presented to our hospital with chief complaint of severe blurry vision with ability to see only shadows upon waking up. Laboratory findings were remarkable for arterial pH of 6.87, $PaCO_2$ 10 mmHg, HCO_3- 5 mmol/ L, AG 45 mmol/L, creatinine 14.4 mg/dL, lactate 20 mm/L, beta-hydroxybutyrate 8 mmol/L, Osmolal gap 52mOsm/Kg. MALA can cause elevated OG likely because of profound lactate and ketoacidosis. It is highly recommended that metformin levels need to be sent out and emergent treatment started including possible HD without waiting for the results.

Keywords: Metformin, Lactic Acidosis, Ketoacidosis, Osmolal Gap, Tissue Hypoxia

INTRODUCTION

The estimated overall prevalence of Diabetes Mellitus (DM) among adults in the United States is 9.5% [1]. Metformin is the principal biguanide in clinical use to control Type 2 Diabetes mellitus (T2DM) owing to its favorable safety profile, low cost and potential pleiotropic benefits such as weight-neutral effect and lower cardiovascular mortality [2,3].

Metformin-Associated Lactic Acidosis (MALA) is a rare side effect of metformin that is primarily seen in patients with renal impairment. Only few cases of coexisting MALA and ketoacidosis have been reported, as case reports typically attribute high anion gap (AG) and osmolal gap (OG) to MALA and uremia [2].

We report a case of combined MALA and ketoacidosis with elevated osmolal gap (OG) in setting of acute kidney injury (AKI) with successful outcome.

CASE PRESENTATION

A 49-year-old man with type 2 DM and hyperlipidemia presented to our hospital with chief complaint of severe blurry vision with ability to see only shadows upon waking up. This was preceded by abdominal pain and hypoglycemia that resolved with juice, the night before. He reported compliance with his home medications which included metformin, Lisinopril, insulin and aspirin. Patient denied illicit drug use and other toxins including antifreeze and home-made alcohol. His last alcoholic intake was 2 days prior to presentation.

In the emergency department, finger stick was 195 mg/dl. Patient was lethargic, dehydrated, tachycardic and tachypnic. Pupils were reactive to light bilaterally but he was not able to follow the examiner's finger. Physical examination was unremarkable otherwise.

Laboratory findings were remarkable for arterial pH of 6.87, $PaCO_2$ 10mmHg, HCO_3- 5 mmol/ L, AG 45 mmol/L, creatinine 14.4 mg/dL, lactate 20 mm/L, beta-hydroxybutyrate 8 mmol/L, Osmolal gap 52 mOsm/Kg. Liver

Corresponding author: Ahmad Kofahi, Department of Internal Medicine, Lincoln Medical Center, Bronx, NY, USA, Tel: 3478038723 E-mail: kofahia@nychhc.org

Citation: Kofahi A, Hishmeh M A, Wasim A, Aldiabat M, Alabdallah K et al. (2020) Combined Metformin-Associated Lactic Acidosis and Starvation Ketoacidosis with High Osmolal Gap. Int J Diabetes Current Res, 2(1): 51-54.

function tests were unremarkable. Ethanol level was undetected. Urinalysis was negative for calcium oxalate crystals. Rest of laboratory findings are presented in **Table 1**. Given the high anion and osmolal gaps, increased beta hydroxybutyrate and increased lactate level, our differential diagnosis on presentation primarily included diabetic ketoacidosis and intoxication with methanol, ethylene glycol, propylene glycol, or metformin. Levels of metformin, isopropyl alcohol, methanol, and ethylene glycol were requested.

Supportive management with intravenous fluids, calcium gluconate, sodium bicarbonate, and mechanical ventilation was started. Poison control center was contacted and fomepizole was recommended for possible methanol toxicity. Emergent hemodialysis (HD) was performed. After one session of HD, electrolytes abnormalities have markedly improved along with improving patient's mental status and vision. See **Table 1** for post-dialysis laboratory findings.

The patient was weaned successfully from mechanical ventilation next day and was discharged home a few days after. Toxicology results came back 2 weeks after initial presentation and were remarkable for metformin levels of 27mcg/ml (therapeutic level <1 mcg/ml) and acetone 15mmol/L. Ethylene glycol, methanol, and isopropyl alcohol were undetected. At subsequent outpatient follow up, patient reported no visual disturbances and his kidney function was back to normal.

Table 1. Overview of laboratory abnormalities before and after hemodialysis.

Laboratory findings on presentation (pre-dialysis), post-dialysis and on day 5				
	Normal Range	**Pre-Dialysis**	**Post-Dialysis**	**Day 5**
Sodium (mmol/L)	135-145	127	139	140
Potassium (mmol/L)	3.6-5.2	5.7	3.6	4.4
Glucose (mg/dL)	70-99	255	163	131
BUN (mg/dL)	7-18	83	55	23
Creatinine (mg/dL)	0.70-1.30	14.4	7.9	1.7
Phosphorus (mg/dL)	2.7-4.5	14.5	3.0	3.1
HCO_3 (mmol/L)	22-26	5	24	28
Anion Gap (mmol/L)	7-14	45	15	10
β-Hydroxybutyric (mmol/L)	0.02-0.27	8.0	2.7	0.3
Lactate (mmol/L)	0.4-2.0	20.4	3.26	1.3
Osmolality (mOsm/Kg)	277-302	350	317	316
Osmolal Gap (mOsm/Kg)	<10	52	10	9
pH	7.35-7.45	6.87	7.47	
$PaCO_2$ (mmHg)	36-44	10	25	

BUN: Blood Urea Nitrogen

DISCUSSION

Metformin is the most commonly prescribed oral antihyperglycemic medication in the world and is considered first line therapy for newly diagnosed Type 2 DM by many professional diabetes organizations [4].

In absence of acute overdose, MALA rarely develops in patients without comorbidities such as renal or hepatic insufficiency or acute infection and is estimated to be 4.3 cases per 100,00 patient-years [5]. Predisposing factors involved in the development of MALA: Vomiting and diarrhea, acute kidney injury, high doses or excessive

accumulation of metformin, and acute disease states leading to tissue hypoxia [5]. While the overall mortality rate of MALA is 25.4% correlating with severity of acidosis, MALA resulting from acute renal failure is associated with a lower Mortality. Non-surviving cases tend to have multiple comorbidities other than renal failure as this is treatable by dialysis [6]. The mechanism of MALA is complex and involves multiple pathways. Metformin promotes the conversion of glucose to lactate in the splanchnic bed of the small intestine [7]. Metformin also inhibits mitochondrial respiratory chain complex-1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine [2], which results in increased lactate and substrate for lactate production [8]. Metformin is excreted from the proximal tubules of the kidneys without being metabolized resulting in its accumulation in renal failure [7].

In the setting of this cellular energy failure, acid-base homeostasis becomes compromised because it is maintained through energy dependent processes such as hepatic gluconeogenesis, which is itself impaired by metformin. These pathophysiologic processes account for severe metabolic acidosis with higher lactic acid levels than typically seen in various types of shock and hypoglycemia, often in the setting of normal or nearly normal hemodynamics.

In cases with lactic acidosis and ketoacidosis related conditions, the OG is mildly elevated, while methanol or ethylene glycol ingestion often leads to more profound rise in OG. MALA, on the other hand, has been associated with mildly elevated OG in some case reports in range of 18-29.3 mOsm/Kg [9-13].

Elevated osmolal gap in setting of MALA can be attributed to an increase in production of ketones [14]· In Metformin toxicity, Metformin-induced inhibition of gluconeogenesis and stimulation of fatty acid oxidation is a likely cofactor for ketogenesis in the absence of other known ketogenic situations [15].

In a previous study by Friesecke et al. [16] overall survival rates for patients with an arterial blood pH of <7.00 was significantly better (50% vs. 0%) in MALA cases when compared with other causes of lactic acidosis. This is primarily due to the fact that MALA is a treatable entity with aggressive interventions, including dialysis especially when recognized early.

As metformin hydrochloride is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions) prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin [17].

Extracorporeal treatment is recommended in severe metformin poisoning. Indications for extracorporeal therapy include lactate concentration greater than 20 mmol/L, pH less than or equal to 7.0, shock, failure of standard supportive measures, and decreased level of consciousness [18,19].

CONCLUSION

MALA can be deadly if not recognized timely but carries good prognosis if suspected and treated early. Though profound elevation in OG is frequently attributed to toxic alcohol intoxication, MALA can cause elevated OG likely because of profound lactate and ketoacidosis. so, it's highly recommended that metformin levels need to be sent out and emergent treatment started including possible HD without waiting for the results.

REFERENCES

1. Pénicaud L, Hitier Y, Ferré P, Girard J, (1992) Glucose metabolism in the splanchnic bed. Br J Pharmacol 105: 1009-1013.
2. National Diabetes Statistics Report (2017) Estimates of Diabetes and Its Burden in the United States. CDC. Accessed on: May 08, 2019. Available online at: Https://www.cdc.gov/diabetes/pdfs/data/statistics/national- diabetes-statistics-report.pdf
3. Vecchio S, Giampreti A, Petrolini VM, Lonati D, Protti A, et al. (2014) Metformin accumulation: lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. Clin Toxicol Phila 52: 129-135.
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359: 1577-1589.
5. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE (2010) Risk of fatal and non-fatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev.
6. Duong JK, Furlong T.J, Roberts DM, Graham GG, Greenfield JR, et al. (2013) The role of Metformin in Metformin-Associated Lactic Acidosis (MALA): Case series and formulation of a model of pathogenesis. Drug Safety 36: 733-746.
7. Renda F, Mura P, Finco G, Ferrazin F, Pani L, Landoni G (2013) Metformin-associated lactic acidosis requiring hospitalization: A national 10-year survey and a systematic literature review. Eur Rev Med Pharmacol Sci 17: 45-49.
8. Sirtori CR, Pasik C (1994) Re-evaluation of a biguanide, metformin: Mechanism of action and tolerability. Pharmacol Res 30: 187-228.
9. Umeda T, Minami T, Bartolomei K, Summerhill E (2018) Metformin-associated lactic acidosis: A case report. Drug Safety Case Rep 5: 8.
10. Lam N, Sekhon G, House AA (2012) Metformin-associated lactic acidosis following intentional overdose successfully treated with tris-hydroxymethyl

aminomethane and Renal Replacement Therapy. Case Rep Nephrol.

11. Tan EM, Kalimullah E, Sohail MR, Ramar K (2015) Diagnostic challenge in a patient with severe anion gap metabolic acidosis. Case Rep Crit Care.
12. Parekh N, Soi S (2011) 239 osmolar gap metabolic acidosis associated with lactic acidosis in patient taking metformin: A case report. Am J Kidney Dis 57.
13. Amin R, Walter R, Bunin J (2013) Metformin Associated Lactic Acidosis mimicking ethylene glycol ingestion in in an alcoholic patient. CHEST 144: 352.
14. Schwetz V, Eisner F, Schilcher G, Eller K, Plank J, et al. (2017) Combined metformin-associated lactic acidosis and euglycemicketoacidosis. Wien Klin Wochenschr 129: 646-649.
15. Schuenemeyer JW (2019) A 35-year-oldwomanwithshock, pulselesselectrical activity arrest, and hemodynamic collapse. CHEST 155: 75-77.
16. Friesecke S, Abel P, Roser M, Felix SB, Runge S (2010) Outcome of severe lacticacidosis associated with metformin accumulation. Crit Care 14: 226.
17. Howlett HC, Bailey CJ (1999) A risk-benefit assessment of metformin in type 2 diabetes mellitus. Drug Saf 20: 489-503.
18. Calelloet DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, et al. (2015) Extracorporeal treatment for metformin poisoning: Systematic review and recommendations from the extracorporeal treatments in poisoning workgroup. Crit Care Med 43: 1716-1730.
19. Duong JK, Furlong TJ, Roberts DM, Graham GG, Greenfield JR, et al. (2013) The role of Metformin in Metformin-Associated Lactic Acidosis (MALA): Case series and formulation of a model of pathogenesis. Drug Saf 36: 733-746.