Scientific Research Publishing

Open Journal of Nephrology, 2023, 13, 195-200
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Diarrhea and Acute Renal Injury Culminating in Metformin-Induced Lactic Acidosis

Kamel El-Reshaid[1*], Abdulmohsen Al-Bader[2]

[1]Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait
[2]Department of Otolarygology, Ministry of Health, Kuwait City, Kuwait
Email: *kamel@hsc.edu.kw

How to cite this paper: El-Reshaid, K. and Al-Bader, A. (2023) Diarrhea and Acute Renal Injury Culminating in Metformin-Induced Lactic Acidosis. *Open Journal of Nephrology*, **13**, 195-200.
https://doi.org/10.4236/ojneph.2023.133018

Received: June 7, 2023
Accepted: July 29, 2023
Published: August 1, 2023

Copyright © 2023 by author(s) and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/

Open Access

Abstract

Background: Metformin (M) is an effective first-line hypoglycemic agent in obese type 2 diabetes mellitus due to its low cost and safety profile. **The Case:** A 66-year-man presented with shock due to lactic acidosis induced by M-supersaturation subsequent to acute renal failure following infective diarrhea. The drug has been used, by this patient, for >10 years without complication. Physical examination, laboratory tests, radiological investigations and blood cultures did not show evidence of new cardiac, hepatic and septic insult. Despite discontinuation of M and 2-days of aggressive hydration, bicarbonate infusions and pressors; toxic levels of the drug persisted and shock-state culminated in severe and oliguric renal failure with serum urea and creatinine up to 50 mmol/L and 1270 umol/L, respectively. Hence, continuous venovenous hemodiafiltration (CVVHDF) was used, for 16-hours, to remove the drug, correct his acidosis and support his severe renal complications. Hours after the procedure; drug level, lactic acidosis and its associated shock improved followed by gradual renal recovery. The patient was discharged after 6 days and serum creatinine reached his base line (180 umol/L) 2 weeks later. The drug was not recommended for his future use. **Conclusion**: M-induced lactic acidosis, should be considered in assessment of shock in M-treated patients and management of unstable patients indicates early-use of CVVHDF.

Keywords

CVVHDF, Diabetes Mellitus, Diarrhea, Lactic Acidosis, Metformin, Shock

1. Introduction

Metformin (M) is an effective first-line hypoglycemic agent in obese patients with type 2 diabetes mellitus (T2DM) [1]. It works by inhibiting the hepatic

production of glucose, reducing its intestinal absorption, and improving its muscle uptake and utilization. Besides lowering the blood glucose level, M may have additional health benefits, including weight reduction, lowering plasma lipid levels, and prevention of some vascular complications [2]. Due to its low cost and safety profile, it has been considered an "essential medicine" by World Health Organization [3]. The most common side effects of M are gastrointestinal viz. epigastric pain, distension, decrease appetite and alteration of bowel movements. However, M induced lactic acidosis (MILA) and its subsequent shock remained an under recognized and rare complication [4]. Moreover, its existence was questioned in metanalysis literature search of 347 trials and cohort studies by Salpeter *et al.* in 2010 [5]. However, emerging case reports and studies confirmed its incidence at 6.3 per 100,000 patient-years and mortality rate up to 50% [6]. MILA is defined as pH < 7.35 and lactate > 5.0 mmol/L in the setting of M-use [4]. In this case report; we describe the emergence of such catastrophic phenomenon in a stable T2DM patient, treated with this drug for >10 years, in an attempt to highlight its predisposition and prevention.

2. The Case

A 66-year-man presented with 2-week history of severe non-bloody diarrhea followed by severe malaise for 2 days. He had T2DM for >15 years. Moreover, he had chronic and stable diabetic renal disease with serum creatinine at 180 umol/L two months prior to admission. His maintenance medications were Glucophage 500 mg twice/daily and Valsartan 160 mg daily for 10 years. He denied recent intake of new medication. On his initial assessment; he was barely responsive to load voice yet able to move all extremities. He was afebrile yet with tachypnea and low blood pressure at 50/20 mm Hg. He was pale yet without cyanosis, lymphadenopathy, oedema, skin lesions and arthritis. Systemic examination did not show other abnormalities. Laboratory investigations showed normal peripheral leucocytic and platelets counts. Hemoglobin was 96 g/L with normal vitamin B12 and transferrin saturation%. G6PD was negative. Peripheral blood smear showed fragmented red blood cells (schistocytes). Serum urea and creatinine were high at 50 mmol/L and 1270 umol/L, respectively. Serum glucose and electrolytes (sodium, potassium, calcium, phosphorus, magnesium) were normal. Serum bicarbonate was 5 mmol/L and arterial blood pH was 6.9 with oxygen saturation at 96%. Liver function tests were normal except for low albumin at 29 g/L. Serum lipids and TSH were normal. Urine routine and microscopy was normal except for 2 (+) proteinuria. ECG showed sinus tachycardia. Chest x-ray was normal. Ultrasound as well as CT scan of abdominal and pelvis did not show abnormality except for bilateral normal-sized kidneys yet with increase cortical echogenicity. Blood cultures were negative for microbial growth. The patient was treated with; 1) discontinuation of Glucophage, 2) Ciprofloxacin 200 mg IV every 12 hours for his infective diarrhea, 3) aggressive hydration with normal saline alternating with bicarbonate infusions, and 4) pressors to support blood pressure. As seen in **Table 1**, over the next 48 hours; 1) acidemia and shock

Table 1. Flow chart of historic biochemical changes with different therapy of the patient with severe lactic acidosis due to Metformin.

Day	1	2	3	4	5	6	14
Laboratory tests:							
Serum urea mmol/L	50	46	42	21	18	12	6
Serum creatinine umol/L	1270	1140	1114	870	621	361	180
Serum metformin umol/L	46			5			
pH	6.9	7	7	7.3	7.3	7.4	7.4
Serum bicarbonate mmol/L	5	6	6	14	18	20	24
Serum lactate mmol/L	5	4	4	2.5	2	1	0.5
Blood pressure mm Hg	50/20	70/40	80/50	100/60	120/70	140/90	140/90
Urine output ml/day	<100	<400	600	800	1500	2000	1600
Therapy:							
IV saline							
IV bicarbonate							
Furosemide							
CVVHDF							

Abbreviations: CVVHDF; continuous venovenous hemodiafiltration.

state persisted, 2) urine output remained poor and a state of massive fluid overload was evolving. Hence; Saline and bicarbonate infusions were held and temporary trial of Furosemide was given prior to using continuous venovenous hemodiafiltration (CVVHDF) for 16 hours. The latter resulted in clearance of fluid overload, uremic intoxication, correction of acidosis with lowering lactate levels. By the 6th day; the patient was stable hemodynamically, biochemically and with good urine output. By the 14th day; his renal function had reached his base line (Table 1). Moreover, results of blood tests arrived later, confirming high M level on admission and its significant decrease after CVVHDF. He was instructed to avoid future-use of M.

3. Discussion

M-toxicity induce hyperlactatemia and subsequent metabolic acidosis through mitochondrial impairment leading to adenosine triphosphate depletion. The latter leads to; 1) accelerated glycolysis, and 2) paralysis of Kreps cycle with accumulation of NADH. Hence, the excessively generated pyruvates are forced to

generate massive amount of lactate, which effluxes into the circulation rather than being gradually oxidized [4]. In a recent systematic search; a total of 242 cases has been reported by 2022 [7]. Furthermore, it showed that accidental or intentional M-intoxication was rare and most (76.4%) had developed in stable type II patients treated with therapeutic doses of the drug. Though the drug is excreted unchanged in the urine; it remains a recommended therapy in mild to moderate renal failure [8]. The dosage guidelines for specific creatinine clearance rates are; 3 g (120 mL/min), 2 g (60 mL/min), 1 g (15 mL/min), and 500 mg (below 15 mL/min) [9]. Based on its pharmacokinetics; renal dysfunction is the major contributing factor for MILA though previous reports showed that only 21% of patients with MILA had underlying kidney disease [7]. Hence, 4 factors should be considered in patients with MILA. The first is that other factors viz. hypotension, dehydration, sepsis, ischemia, and liver impairment, which lead to increased production or impaired clearance of lactates, may also contribute to lactic acidosis. The second is the existence of an inter-individual genetic variation in OCT2 (gene SLC22A2) leading to different MF pharmacokinetics and variable toxicity levels [10]. The third is de novo precipitating risk/s in an otherwise stable T2DM patient that include; acute gastroenteritis leading to dehydration, ACEI/ARB leading to decrease renal perfusion, nephrotoxic drugs e.g., aminoglycosides, NSAIDs and anti-retroviral drugs like tenofovir, overzealous-use of diuretics, IV contrast, post-operative, acute urinary tract infection or obstruction [7]. The fourth is renal hypoperfusion following any shock state viz. sepsis, anaphylactic as well as heart and liver failure. In our patient; progressive dehydration due to his infective diarrhea and Valsartan-induced renal hypoperfusion induced M-supersaturation leading to lactic acidosis and shock which was refractory to volume repletion and pressors. Such shock state perpetuated his renal failure leading to prolonged M-toxicity and limited his conservative management. Extracorporeal therapy for M-removal and its associated MILA-shock is indicated if lactate levels above 20 mmol/L, pH less than 7.0, presence of shock, reduced consciousness or in patients with failure of standard supportive measures. It can be discontinued if serum lactate levels fall below 3 mmol/L and the pH becomes more than 7.35 [11]. The current extracorporeal therapy include; intermittent hemodialysis (preferably with high-flux/high-efficiency dialyzers) and CVVHDF. The first is more practical with less operating cost and need for intensive care monitoring while the second is the ideal for shocked patients with/without co-morbidities [11]. Finally; our patient had few though serious short-term complications of his MILA with severe oliguric renal failure and fluid overload as well as hemolytic anemia. Previous case reports/series have described; encephalopathy, psychosis, hemolytic anemias, acute pancreatitis, cardiac arrest as well as chronic liver and renal disease [7]. Such complications were closely related to; 1) delay in diagnosis of MILA and/or its inadequate management, and/or 2) its associated co-morbidities. Since the prognosis of lactic acidosis primarily depends on the underlying mechanism and on its reversibility [12]. Finally; the therapeutic concentration of M is not well defined and

can range from 0.1 to 20.7 (median 4.5) umol/L by high-performance liquid chromatography system [13]. If M-toxicity is suspected; patients should be treated as M-associated lactic acidosis (MALA) since drug level test is usually delayed or unavailable in most centers.

4. Conclusion

MILA can develop with therapeutic doses of MF. Early diagnosis, management of precipitating insults and extracorporeal support are associated with favorable outcomes.

Statement of Ethics

The case was reported according to World Medical Association Declaration of Helsinki. There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of Intensive Blood-Glucose Control with Metformin on Complications in Overweight Patients with Type 2 Diabetes (UKPDS 34). *Lancet*, **352**, 854-865. https://doi.org/10.1016/S0140-6736(98)07037-8

[2] DeFronzo, R.A. and Goodman, A.M. (1995) Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus. The Multicenter Metformin Study Group. *The New England Journal of Medicine*, **333**, 541-549. https://doi.org/10.1056/NEJM199508313330902

[3] American Diabetes Association (2020) Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes*—2020. *Diabetes Care*, **43**, S98-S110. https://doi.org/10.2337/dc20-S009

[4] DeFronzo, R., Fleming, G.A., Chen, K. and Bicsak, T.A. (2016) Metformin-Associated Lactic Acidosis: Current Perspectives on Causes and Risk. *Metabolism*, **65**, 20-29. https://doi.org/10.1016/j.metabol.2015.10.014

[5] Salpeter, S., Greyber, E., Pasternak, G. and Salpeter, E. (2002) Risk of Fatal and Nonfatal Lactic Acidosis with Metformin Use in Type 2 Diabetes Mellitus. *Cochrane Database of Systematic Reviews*, **2**, CD002967. https://doi.org/10.1002/14651858.CD002967

[6] Renda, F., Mura, P., Finco, G., Ferrazin, F., Pani, L. and Landoni, G. (2013) Metformin-Associated Lactic Acidosis Requiring Hospitalization. A National 10-Year Survey and a Systematic Literature Review. *European Review for Medical and Pharmacological Sciences*, **17**, 45-49.

[7] Juneja, D., Nasa, P. and Jain, R. (2022) Metformin Toxicity: A Meta-Summary of Case Reports. *World Journal of Diabetes*, **13**, 654-664. https://doi.org/10.4239/wjd.v13.i8.654

[8] Inzucchi, S.E., Lipska, K.J., Mayo, H., Bailey, C.J. and McGuire, D.K. (2014) Metformin in Patients with Type 2 Diabetes and Kidney Disease: A Systematic Review. *JAMA*, **312**, 2668-2675. https://doi.org/10.1001/jama.2014.15298

[9] Duong, J.K., Kumar, S.S., Kirkpatrick, C.M., Greenup, L.C., Arora, M., *et al.* (2013) Population Pharmacokinetics of Metformin in Healthy Subjects and Patients with Type 2 Diabetes Mellitus: Simulation of Doses According to Renal Function. *Clinical Pharmacokinetics*, **52**, 373-384. https://doi.org/10.1007/s40262-013-0046-9

[10] Gong, L., Goswami, S., Giacomini, K.M., Altman, R.B. and Klein, T.E. (2012) Metformin Pathways: Pharmacokinetics and Pharmacodynamics. *Pharmacogenet Genomics*, **22**, 820-827. https://doi.org/10.1097/FPC.0b013e3283559b22

[11] Calello, D.P., Liu, K.D., Wiegand, T.J., Roberts, D.M., *et al.* (2015) Extracorporeal Treatments in Poisoning Workgroup. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations from the Extracorporeal Treatments in Poisoning Workgroup. *Critical Care Medicine*, **43**, 1716-1730. https://doi.org/10.1097/CCM.0000000000001002

[12] Friesecke, S., Abel, P., Roser, M., Felix, S.B. and Runge, S. (2010) Outcome of Severe Lactic Acidosis Associated with Metformin Accumulation. *Critical Care*, **14**, R226. https://doi.org/10.1186/cc9376

[13] Frid, A., Sterner, G.N., Löndahl, M., Wiklander, C., Cato, A., *et al.* (2010) Novel Assay of Metformin Levels in Patients with Type 2 Diabetes and Varying Levels of Renal Function: Clinical Recommendations. *Diabetes Care*, **33**, 1291-293. https://doi.org/10.2337/dc09-1284