Metformin – associated lactic acidosis treated with Continuous Renal Replacement Therapy in a critically ill patient: Case report and review of the literature

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ABSTRACT

Metformin – associated lactic acidosis treated with Continuous Renal Replacement Therapy in a critically ill patient: Case report and review of the literature.

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Though metformin is considered as first choice drug in type II diabetes, clinicians should be alert both for presence of potential contraindications to its use and to possible adverse reactions. Bad therapy compliance along and/or concomitant comorbidities may lead to serious toxicity. We hereby describe a case of extreme lactic acidosis- associated with metformin therapy- in an elder woman, managed with Continuous Renal Replacement Therapy in Intensive Care Unit environment. Short review of the literature about the place of renal replacement therapy in such cases is also discussed.

INTRODUCTION

Available since 1985, metformin has gained its place in clinical practice as first-line treatment in adults with type II diabetes melitus. It can be used either as monotherapy or combination therapy with glucagon-like peptide-1 receptor agonist (GLP-1 RA), sodium-glucose co-transporter inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP4-I), thiazolidinedione (TZD), sulfonylurea (SU), and insulin[1]. Moreover, today its use is recommended in prediabetes[2,3], type I diabetes melitus[2,4], gestational diabetes melitus, polycystic ovary syndrome[2,5]. At the same time, there are a lot of reports about its cardioprotective and neuroprotective effects, its antitumor and antiaging effects; and its positive results as secondary prevention strategy for antipsychotic-related weight gain[2].

Metformin adverse reactions include mainly (up to 20%) gastrointestinal intolerance and taste

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sense change, while hypoglycaemia, allergic reactions and hypothyroidism are rare[2]. Vitamin B_{12} deficiency and lactic acidosis are considered as very rare side effects. The later has worse progress when it is associated with presence of infection, dehydration or concomitant use of diuretics. Though rare, mortality approaches 30-50 %[6].

We hereby describe a case of extreme type B lactic acidosis associated with metformin therapy in an elder woman, managed with Continuous Renal Replacement Therapy in Intensive Care Unit environment.

CASE REPORT

A 72-years old female patient was transported to Emergency Department (ED) due to weakness, dizziness, shortness of breath, loss of appetite, nausea and oliguria. Her medical history included obesity (ICD_{10}- E66) with BMI – 37 kg/m^2, type II diabetes mellitus (ICD_{10}-E11.8) under metformin 850 mg b.i.d., arterial hypertension (ICD_{10}-I10) under olmesartan medoxomil/hydrochlorothiazide 20 mg/12.5 mg o.d. and dyslipidemia (ICD_{10}- E78.5) under rosuvastatin 20 mg o.d.; yet with bad compliance to drug therapy. Initial clinical examination revealed hypotension (Blood Pressure - 60/25 mmHg), tachycardia (Heart Rate – 105 bpm), tachypnoea (Respiratory rate of 35 bpm) with measured SpO_2 in air of 95% and a Glasgow Coma Scale (GCS) of E3/V4/M6. Yet, her initial arterial blood gases (ABG) analysis revealed a serious lactic acidosis. During her ED ealuation, her mental status decreased rapidly to GCS E2/V2/M3, thus Rapid Sequence Intubation (RSI) where performed and the patient was admitted at Intensive Care Unit. Calculated initial severity scores were: APACHE (Acute Physiology and Chronic Health Evaluation) II 39, APACHE IV 156, SAPS II (Simplified Acute Physiology Score) 86 and SOFA (Sequential Organ Failure Assessment) score 15.

Upon admission, aggressive treatment with fluids, bicarbonate administration and inotropic therapy (noradrenaline 1.2 μg/kg/min c.i.v. and adrenaline 0.3 μg/kg/min c.i.v.). However, anuria and severe metabolic acidosis continued and decision for CRRT (continuous renal replacement therapy) was taken. The patient was put on CVVHDF (Continuous Venovenous Hemodiafiltration) which continued for 45 hours with progressive correction of acidosis. Selected laboratory and ABG exams during her ICU hospitalization are displayed in Tables 1 and 2 respectively.

The rest of her drug regiment included empiric antibiotic prophylaxis, gastric ulcer antithrombotic prophylaxis.

Clinical and laboratory improvement continued slowly after the cessation of CRRT, inotropic drug infusions were stopped the following 4 days and at 11^{th} day of hospitalization mechanical ventilation discontinued, and the patient was extubated.

Table 1. Selected Laboratory exams during ICU hospitalization. The rest of the examined parameters (lactate dehydrogenase, amylase, alkaline phosphatase, γ-glutamyl transferase, liver transaminases) were within normal values.

Day	Hct	Hb	PLT	WBC	CRP	PCT	Glu	Cr	Ur	BUN
1st	31.6	9.6	235	23.16	0.1	0.32	326	10.6	194	90.54
2nd	32.6	10.7	243	27.77	0.2	0.81	132	6.8	141	65.8
3rd	27.4	9.4	182	17	5	3.58	96	2.31	51	23.8
4th	25.6	8.9	140	12.85	5.2	2.55	158	2.44	45	21
5th	25.6	8.9	148	13.9	6.3	1.51	145	3.08	56	26.13
7th	24.8	8.5	160	11.4	8.2	0.67	149	4.53	79	36.87
9th	23.3	8	264	9.34	11.7	0.34	74	4.97	84	39.2
10th	23.1	7.6	216	8.88	6.2	0.13	115	2.39	42	19.6
11th	25.6	8.4	285	12.82	6.9	0.22	120	2.93	67	31.27
14th	27.2	8.8	382	11.62	1.8	0.12	103	2.38	81	37.8

Day	Na^+	K^+	Ca^{+2}	Phos	Pr_{tot}	Alb	CPK
1st	137	5.8	7.6	11.7	5.3	3.1	53
2nd	141	4	7.7	7.3	5.4	3.2	79
3rd	138	4.6	7.7	3.5	4.9	3	362
4th	139	4.2	7.7	1.4	4.4	2.7	468
5th	140	5.1	7.5	2.6	4.8	2.4	738
7th	143	4.1	7.4	2.6	4.2	2.3	345
9th	147	4	7.7	2.2	4.4	2.4	54
10th	142	4	8.4	1.6	4.9	2.4	60
11th	145	4.3	8.1	3.5	4.7	2.7	68
14th	150	4.6	7.7	3.5	5.2	3	71

Hct- haematocrit (%), Hb- haemoglobin (g/dl), PLT-platelets (k/μl), WBC- white cells (k/μl), CRP- c reactive protein (mg/dl), PCT-procalcitonin (ng/ml), Glu- glucose (mg/dl), Cr – creatinine (mg/dl), Ur -urea (mg/dl), BUN- blood urea nitrogen (mg/dl), Prtot- Protein total (g/dl), Alb- albumin (g/dl), CPK- creatine phosphatase (mg/dl).

Table 2. Time course of Arterial Blood Gases exams during ICU hospitalization.

A.

Time	pH	PaO_2	FiO_2	$PaCO_2$	HCO_3	Lac	BE	AGc	ΔGc	Δ/Δ ratio	SIDa	SIDe	SIG
ED	6.67	73.7	35	15.1	1.6	17	-30.3	22.75	10.75	0.38	12.4	5.21	5.19
20 min	6.63	159	99	27.8	2.8	16	-29.7	31.05	19.05	0.79	19.6	5.62	13.98
30 min	6.69	115	85	35	4	14.6	-27.8	28.25	16.25	0.7	20.9	7.61	12.71
40 min	**6.609**	**157**	**99**	**34.4**	**3.2**	**16**	**-29.3**	**30.35**	**18.35**	**0.77**	**19.5**	**6.08**	**13.05**
4 h	**6.99**	**64.5**	**85**	**32.6**	**7.4**	**13.9**	**-21.6**	**24.75**	**12.75**	**0.63**	**21.6**	**16.04**	**5.04**
8 h	**7.11**	**55**	**90**	**29**	**9**	**10.7**	**-18.6**	**23.25**	**11.25**	**0.6**	**25.8**	**19.41**	**6.89**
16 h	**7.25**	**137**	**35**	**23.6**	**10**	**7.3**	**-15.8**	**21.25**	**9.25**	**0.5**	**29.7**	**22.53**	**8.17**
24 h	**7.28**	**151**	**35**	**21**	**9.8**	**5.7**	**-15.7**	**20.6**	**8.6**	**0.46**	**30.3**	**23.37**	**6.93**
32 h	**7.32**	**161**	**35**	**22**	**11.3**	**2.3**	**-13.7**	**20**	**8**	**0.43**	**33.7**	**24.72**	**8.98**
45 h	**7.33**	**135**	**35**	**36**	**18.7**	**2**	**-6.1**	**15.5**	**3.5**	**0.19**	**36**	**31.7**	**4.3**

B.

Day	pH	PaO_2	FiO_2	$PaCO_2$	HCO_3^-	Lac	BE	AG	ΔG	Δ/Δ ratio
3rd	7.46	141	30	27	19.1	1.3	-4.1	10	-2	-0.41
4th	7.34	89.9	30	42.4	22.3	0.9	-2.5	7	-5	-2.94
5th	7.39	132	30	37.9	22.8	1.1	-1.4	6.4	-5.6	-4.67
6th	7.47	117	30	32.7	23.8	0.9	0.8	7.8	-4.2	-21
7th	7.45	119	30	35.7	24.8	1.1	1.3	8.6	-3.4	4.25
8th	7.39	142	30	42.6	25.7	0.9	1.4	7.6	-4.4	2.588
9th	7.37	139	30	45.7	26.2	0.7	1.6	5.9	-6.1	2.773
10th	7.35	82.7	40	47.3	25.9	0.6	1	9.4	-2.6	1.368
11th	7.42	95.2	40	39.2	25.1	0.5	1.1	8.6	-3.4	3.091
12th	7.44	69.7	40	38.1	25.7	0.9	2	7.6	-4.4	2.588
13th	7.42	108	41	35.6	22.9	0.6	-0.9	9.7	-2.3	-2.09
14th	7.43	140	41	35.4	23.3	0.9	-0.4	9.1	-2.9	-4.14

PaO_2- arterial Partial Oxygen pressure (mmHg), $PaCO_2$- arterial partial carbon dioxide pressure (mmHg), FiO_2 -fraction of inspired oxygen (%), HCO_3^-bicarbonates (mEq/l), Lac- Lactate (mmol/l), BE – base excess, AGc – anion gap corrected, ΔGc -delta gap corrected, Δ/Δ -delta delta ratio, SIDa- Strong Ion Difference actual, SIDe – strong ion difference estimated, SIG – strong Ion Gap. Bold values represent ABG during CVVHDF.

Two days later she was discharged from ICU without any sequels.

DISCUSSION

Metformin-associated lactic acidosis (MALA) refers to blood lactate concentrations greater than 5 mmol/L and arterial pH less than 7.35 in association with metformin exposure[7]. A newer definition system recognises three conditions: a. MALA, where metformin amplifies the degree of lactic acidosis, but it is not the sole cause of illness; usually there are other contributing co-morbidities. b. MULA metformin unrelated lactic acidosis, where metformin is just an innocent bystander; yet, metformin blood levels are necessary to distinguish from MALA and c. MILA – metformin induced lactic acidosis, where high levels of metformin are the primary cause of acidosis. MILA can be either acute poisoning in absence of renal dysfunction or subacute accumulation due to renal failure[8].

The latter is what we suggest that was the toxicity mechanism in our case: we presume that diabetic nephropathy was already in progress; and that along with bad compliance to therapy, metformin resulted a high anion gap type B lactic acidosis.

The mechanism of MALA is complex. Metformin promotes the conversion of glucose to lactate in the splanchic bed of the small intestine. It also inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate and alanine. This results in additional lactate and substrate for lactate production[7-8].

Initial therapy is resuscitation and supportive care. Gastrointestinal decontamination (use of active charcoal) is only an early option. Bicarbonate has been used but concerns are raised about the possibility of worsening intracellular acidosis. Thus, it is considered as an option only in extremely low bicarbonate levels (<5mEq/l); as in our case[7]. Glucose management and volume resuscitation included Actrapid® 8 ui i.v. bolus once and mainly NaCl 0.9% infusion (along with bicarbonate). Literature present various approaches: A case series of three patients with metformin-associated lactic acidosis and concurrent euglycemic DKA reported clinical improvement when treated with glucose infusion and dialysis alone (without an insulin infusion)[9]. Volume resuscitation options include either D_5W with 1/2 NaCl 0.9%, plus 50 mEq of bicarbonate added per liter or simultaneous infusions of normal saline and isotonic bicarbonate. Insulin therapy may be beneficial; yet Glucose, Insulin, Potassium ("GIK") therapy is generally not recommended[10].

Though often reported, there is lack of solid guidelines regarding the use CRRT for MALA. EXTRIP[11] guidelines suggest several indications for starting and ending CRRT in those cases (Table 3).

Table 3. Extra corporeal therapy recommendations (ECTR) for MALA[11].

General ECTR is recommended in severe metformin poisoning (1D)
Indications ECTR is recommended if
Lactate concentration > 20 mmol/L (180 mg/dL) (1D)
Blood pH ≤ 7.0 (1D)
Standard therapy (supportive measures, bicarbonate, etc.) fails (1D)
ECTR is suggested if
Lactate concentration is 15–20 mmol/L (135–180mg/dL) (2D)
Blood pH 7.0–7.1 (2D)
Comorbid conditions that lower the threshold for initiating ECTR
Impaired kidney function (1D)
Shock (1D)
Decreased level of consciousness (2D)
Liver failure (2D)
Cessation of ECTR is indicated when Lactate concentration is < 3 mmol/L (27mg/dL) and pH > 7.35 (1D)
Choice of ECTR
As an initial ECTR, intermittent HD with bicarbonate buffer is preferred (1D), but CRRT is an acceptable alternative if HD is not available (2D) After the initial ECTR session, either HD(1D) or CRRT (1D) is appropriate if necessary.

HD- hemodialysis

Mode of CRRT chosen varies from haemodialysis, sustained low efficiency dialysis (SLED), continuous hemofiltration (CVVH) to CVVHD; with survival rates from ICU patients with MALA undergoing CRRT reaching in some reports to 80%[12]. Adopted dialysis policy of early, extended, continuous, and high efficiency CRRT could have contributed to the reported positive results. On the other hand, there are also reports of cases refractory even to haemodialysis therapy in the setting of concomitant alcohol[13].

Finally, other suggested rescue therapy options as methylene blue, are still controversial[7].

CONCLUSION

Since patients under metformin therapy are a large part of diabetic population, clinicians should be alert about the possibility of MALA. Early diagnosis, resuscitation measures and an early dialysis (HD of CRRT) therapy could

contribute to successful outcome. Furthermore, increasing report rate could help improve existing therapy guidelines for such cases.

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