STEPHY Publishers

Trends in Urology and Nephrology Research

Case Report

ISSN: 2995-3871

Metformin Associated Lactic Acidosis (MALA Syndrome): A Case Report

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Abstract

Metformin is the most commonly prescribed drug to treat diabetes in the world: its action is based on activation of AMPK chinase with different metabolic effects, such as reduction of gluconeogenesis, increases peripheral uptake of glucose, and decreases fatty acid oxidation. Lactic acidosis is the most frequent cause of metabolic acidosis associated at use of metformin and the risk increases accumulation in presence of precipitating factors as acute kidney injury or dehydration. The presence of chronic kidney disease increases the risk of MALA syndrome.

Keywords: Metformin, MALA syndrome, AKI, Acute kidney injury, Lactic acidosis

Introduction

Metformin is the most commonly prescribed oral antihyperglycemic medication in the world and is considered first line therapy for newly diagnosed type 2 diabetes by many professional diabetes organizations. Metformin is generally regarded as safe drug: the most frequent adverse effects caused on gastrointestinal system (diarrhoea, nausea, and to a lesser extent, vomiting): in particular, metformin is less well tolerated in patients with preexisting gastrointestinal conditions:[1] it is included in the class of biguanides that also included phenformin and buformin, withdrawn from most pharmaceutical markets due to the elevated risk of causing lactic acidosis.[2]

Biguanides have a well-defined effect on glucose/lactate metabolism, which actually contributes to their antidiabetic properties and is believed to result from the blockade of gluconeogenic precursors, such as lactate and alanine, to pyruvate. This effect is absent in all other classes of antidiabetic drugs. Metformin has multiple mechanisms of action, not exactly understood: it reduces gluconeogenesis, increases peripheral uptake of glucose, and decreases fatty acid oxidation. The inhibition of mitochondrial complex I results in defective cyclic adenosine monophosphate (cAMP) and protein kinase A signalling in response to glucagon.

From a pharmacokinetic point of view, metformin is little bounded at plasma proteins and unmetabolized excreted in the urine, without direct nephrotoxic action. The half-life is approximately 6.5 h in individual with normal renal function, extending in patients with severe renal failure. Lactic acidosis is the most frequent cause of metabolic acidosis (metformin associated) characterized by an increase in the anion gap (the blood concentration of sodium minus the concentrations of chloride and bicarbonate). The standard working definition is an arterial lactate concentration exceeding 5 mmol/L and pH <7.35. Cases of lactic acidosis are conventionally classified as anaerobic (type A) or aerobic (type B): however, this distinction has become obsolete, since a restricted oxygen supply and metabolic factors often act simultaneously.[3]

Two different types of lactic acidosis, related to metformin therapy, have been proposed. In particular, MALA (metformin-

Quick Response Code:

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Received: 22 October, 2024 **Published:** 05 November, 2024

Citation: De Stefano F, Di Nuzzi L, Simiele S, Grimaldi M, De Lucia F. Metformin Associated Lactic Acidosis (MALA Syndrome): A Case Report: Case Report. *Trends Uro Nephro Res.* 2024;3(1):1–4. DOI: 10.53902/TUNR.2024.03.000513

associated lactic acidosis), is caused by metformin accumulation in presence of precipitating factors (for example acute kidney injury or dehydration); less common is MILA (metformin-induced lactic acidosis), when metformin seems to be the only cause of lactic acidosis without apparent associated pathology and is usually related to acute intoxication. MALA syndrome, strictly defined by arterial lactate >5 mmol/L and blood pH <7.35 with high anion gap, within the context of recent metformin exposure, represents a rare but worrisome complication, with a mortality rate ranging from 10% to 45%. Identified risk factors for MALA include acute kidney injury, hypoxemia, sepsis, alcohol abuse, liver failure, radiological contrast media administration, myocardial infarction, and shock. Moreover, medications that interfere with renal hemodynamic autoregulation (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretic, non-steroidal anti-inflammatory drugs) and volume depletion, secondary to gastrointestinal losses or inappropriate hydration, are frequently implicated in generating acute kidney injury leading to MALA.[4]

However, high serum levels of metformin (4 mg/L is considered the high side of the target range) interfere with mitochondrial respiratory chain complex and then with the oxidative metabolism of lactate, inducing a non-hypoxic lactic acidosis.[5] Though the prevalence of metformin-associated lactic acidosis (MALA) is low, mortality is high, ranging from 25-50%. Therefore, it presents a diagnostic challenge that is critical to identify, particularly in patients with renal impairment at baseline.[6] The relationship between metformin and lactic acidosis is currently a subject of debate; despite the recent Cochrane review.[7] In which no contraindications were provided against administering metformin, 11 several authors have provided evidence for a relationship between this drug and the development of this important complication, when metformin was added. Vecchio recently demonstrated that metformin plasma concentrations were closely correlated with creatinine, pH, and plasma lactate levels, whereas lactate and metformin mean values were not statistically different in surviving and deceased patients.[8]

Case Report

Here describes a case of man of sixty-three years, diabetic and hypertensive patient from twenty years without heart disease, who accesses in our hospital emergency division at night, referring nausea, lack of appetite and vomiting from 48 hours, anuria from eighteen hours, no edema, with those clinical parameters: BP [150/90 mmHg], HR [110 bpm], SpO_2 [92 %]. At electrocardiogram: sinusal tachycardia without sign of early ventricular repolarization. The patient reports no kidney injuries and normal serum level of creatinine, urea and absence of proteinuria. The biochemical parameters were: HCO_3 [4.3 mmEq], Lactates [16.5 mmol/L], pCO_2[8 mmol/L], sCreatinine [9.31 mg/dL], sUrea[145 mg/dL], sK^+ [5.79 mEq/L], Anion GAP [43 mmol/L]. His daily therapy before hospital access: Metformin 2g/die (1 gr at lunch, 1 gr at dinner), Olmesartan 40 mg/die, ASA 100mg.

We suspected MALA syndrome: AKI (acute kidney injury) with lactic acidosis with high anion gap and so the patient undergoes a positioning of venous femoral catheter to start the haemodialysis session. We decided to start haemodialysis in bicarbonate dialysis mode of 240 minutes with this dialytic bath: Na [143 mmol/L], HCO_3 [36 mmol/L], K^+[3.0 mmol/L], Ca^{2+}[1.5 mmol/L], blood-flow [220 mL/min], dialytic-flow [500 ml/min] and Ultrafiltration Rate [200 mL/h]. During the bicarbonate dialysis session prescribed infusion of isotonic saline solution with concentration of NaCl 0.9% at rate of 200 mL/h, and Oxygen therapy with FiO_2 at 28% in Venturi Mask. We used as dialyzer Fresenius Fx 60 with sintetic membrane Helixone (made in polisulfone) which demonstrated a higher dialytic efficacy, biocompatibility and a better clearance of uremic toxins, leading a high flux haemodialysis.[9] We used as We measured the blood pressure before dialytic session, during the session (range of 15 minutes) and after session and made an arterial blood gases sampling each hour to value acid-base equilibrium and lactataemia. At the end of first dialysis session the blood gas analysis showed: HCO_3 [26 mmEq], Lactates [4.5 mmol/L], pCO_2 [28 mmol/L], sK^+ [3.2 mEq/L], Anion GAP [9 mmol/L]. After 24 hours we confirmed a new session of bicarbonate dialysis with the same parameters and finally diuresis started (300 mL at the end of session); so, we interrupted the haemodialysis program and observed a reduction of serum lactates and a reduction of respiratory compensation of metabolic acidosis Figures 1.

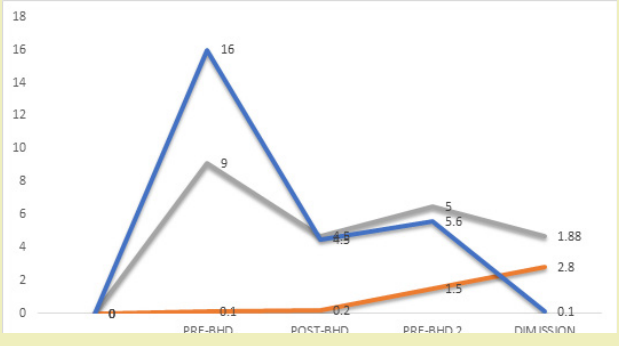

Figure 1: Variation of serum creatinine, with diuresis and Lactates in time

The recovery of spontaneous diuresis changed the prognosis of the patient because the excretion of metformin is through urine output without any metabolism changing, thus allowing the total elimination of the remaining dose of drug. The increased elimination of metformin however determined the improvement of serum parameters and the reactivation from ischaemia the nephrons units.

Thus, the rehydration therapy using isotonic crystalloids solution with concentration of NaCl 0.9%, Sodium Bicarbonate 8.4% as hypertonic solution to correct the serum bicarbonates deficit and Ringer Lactate (isotonic) crystalloids solution, allowed to correct total water deficit. Furthermore, during the recovery, the patient started insulin therapy to control serum glucose.

Furthermore, an important instrument to evaluate the functional recovery from kidney injury during MALA syndrome are ultrasound and Doppler signal: reducing of parenchimal vascularization, reduced cortical thickness and increased echogenicity of renal medulla are factors of worsening prognosis. At the exam we saw two kidneys of approximately 110 mm of longitudinal diameter, cortical and medulla not hyperechoic, cortical-medulla thickness of 17 mm (normal range), vascularization in normal range. These results demonstrated the function recovery of kidneys. Finally, the patient discharged in optimal clinical conditions after five days of hospitalization, with those serum values: HCO_3 [25 mmEq], Lactates [0.1 mmol/L], pCO_2 [36 mmHg], sCreatinine [1.88 mg/dL], sUrea [60 mg/dL], sK^+ [3.77 mEq/L]. At urinalysis presented a Protein-Creatinine Ratio of 180 mg/dL. The clinical parameters were: BP [125/80 mmHg], HR [68 bpm], SpO_2 [99%] Table 1.

Table 1: Serum and acid-base parameters. **A.** Before first dialysis session. **B:** Before second dialysis session. **C:** Six Hour after the start of diuresis. **D:** Before the discharging

Parameters	Pre-BHD	Post BHD	Pre- BHD 2	Dimission	Control
Creatinine	9 mg/dL	4.5 mg/dL	5 mg/dL	1.88 mg/dL	1.85 mg/dL
Urea	145 mg/dL	68 mg/dL	88 mg/dL	60 mg/dL	58 mg/dL
K+	5.79 mEq/L	3.2 mEq/L	4 mEq/L	3.77 mEq/L	3.95 mEq/L
pCO2	8 mmHg	28 mmHg	33 mmHg	36 mmHg	38 mmHg
Lactates	16 mmol/L	4.5 mmol/L	5.6 mmol/L	0.1 mmol/L	0.1 mmol/L
Anion Gap	43 mmol/L	9 mmol/L	12 mmol/L	5 mmol/L	5 mmol/L
Bicarbonate	4.3 mmol/L	26 mmol/L	22 mmol/L	25 mmol/L	24 mmol/L

The only drug changed at discharging is the metformin, replaced by insulin initially and then prescribed Dapagliflozin 10 mg, a Sodium-Glucose-Transportes-Inhibitor with Dipeptidil-dipeptidase inhibitor like Linagliptin 5 mg; Olmesartan reduced at 10mg/die. We prescribed also a blood pressure 24 hours control and nephrologist follow up at 60 days.

After 60 days the patient returned to nephrological visit in good condition and with serum parameters: HCO_3 [24 mmEq], Lactates [0.1 mmol/L], pCO_2 [38 mmHg], sCreatinine [1.85 mg/dL], sUrea [58mg/dL], sK^+ [3.95mEq/L].

Discussion and Conclusions

Metformin is dialysable. It circulates without binding to protein and has a very large distribution: mean values of volume of distribution is between 63 and 276 litres. Normally after oral dose of 1000 mg, half-life elimination is 6.5 hours and the drug is removing through the kidney: the clearance is higher than 400mL/min by glomerular filtration and tubular secretion. Thus, dialysis treatment is the most effective method in terms of both removing the drug and solving the acid-base problem. The choice of type of dialysis treatment is based on hemodynamic status of patient: we preferred in unstable patient continuous-veno-venous-hemodialfiltration (CVVHDF) or hemodialysis (CVVHD).[9]

In this case, we chosen bicarbonate dialysis treatment, but we educated our nursing staff on monitoring blood pressure at range of 15 minutes and withdrawing an arterial blood sampling each hour: it's very important to avoid hypotension and so a more reduction of renal perfusion, worsening the grade of ischemia of nephrons. The control of acid base equilibrium instead, helped us to value the modification of serum bicarbonate and lactates so to modify the dialytic prescription if necessary. The recovery of diuresis it's the most important event during lactic acidosis: the recovery of nephron allows the excretion of acids e reabsorption of bicarbonates to buffer the acidosis and increases also the clearance urinary of metformin. The recovery of diuresis can be explained in three ways: metformin can be removed from plasma by dialysis membrane, lactic acid is buffered by bicarbonate and the infusion of saline solution allows the maintenance of renal and glomerular perfusion, so to pretend the ischemia of nephrons.

A retrospective analysis study compared cases of severe acidosis with pH <7.0 secondary to MALA syndrome and lactic acidosis of other origins. It shows that despite a greater degree of acidosis and renal failure in MALA patients, early recognition and aggressive medical therapy including renal replacement therapy improves the survival.[10] A recent review article suggests that given the mild association between metformin and lactic acidosis, metformin can be used in those with impaired renal function but should be dosed by Glomerular filtration rate.[11]

The importance of nephrologist point of view for management of diabetic patients, leading to an improvement of survival of these patients, above all on the administration of kidney complications during diabetic disease: chronic kidney disease, proteinuria, electrolytes disorders and therapies management and dosage adjustment. The risk of MALA syndrome in diabetic patient with metformin can be reduced or avoided through nephrologist follow up, which could be started when diabetic diagnosis has made and not when started kidney damage.

Lately the use of metformin in the diabetic people is reducing because the new drug therapies of diabetes are widely used: such as sodium-glucose-transporter-inhibitors and Dipeptidil-dipeptidase-IV-inhibitors or the GLP-1 agonist drugs that are proving a reducing of cardiovascular risk and above all the stabilization of glomerular rate with slowdown of chronic kidney disease over time.[12] This new therapies, as well as metformin work on basal metabolism and cause a reduction of weigh in time: sometimes the diabetic patient is obese and it's important to act on obesity reducing cardiovascular risk; the important difference is that lactic acidosis is not reported in the studies of sodium-glucose-transporter-inhibitors (iSGLT) Dipeptidil-dipeptidase-IV-inhibitors (iDPP-IV) or the GLP-1 agonist (aGLP-1).[13]

Acknowledgements

None.

Funding

All authors declared no sponsorship or funding arrangements relating to the study.

Conflict of Interest

All authors declared no conflict of interest. The patient gave written consent to use its clinical data.

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