CLINICAL CASE

RARE CASE OF LIFE-THREATENING METFORMIN-ASSOCIATED ACIDOSIS WITHOUT HYPERLACTATEMIA IN POSTOPERATIVE PERIOD

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ABSTRACT

Metformin belongs to the biguanide class and is used in lowering serum glucose levels in diabetic patients. Metformin-associated lactic acidosis (MALA) is a severe and potentially fatal complication. The aim of this article is to emphasize the importance of early symptom recognition and prevention measures in patients on metformin. We report the case of a 90-year-old female patient admitted for major orthopedic surgery who developed MALA but with normal lactate levels post-intervention due to escalating renal impairment in the context of surgical stress. Intoxication was promptly resolved with fast-responding intravenous bicarbonate. If not adequately managed, MALA can be avoided if systemic drug exposure is limited in patients at risk. Rational administration of metformin should be implemented, knowing it currently belongs to the first-line therapeutical options in diabetic patients.

KEYWORDS: *metformin, lactic acidosis, type II diabetes mellitus, normal lactate*

INTRODUCTION

Metformin, a biguanide derived from a natural herbal product named galegine, is one of the most prescribed oral antidiabetics, considered to be the first line agent in treating type II diabetes due to its efficacy, good safety profile and capacity to be associated with other antidiabetic agents [1]. The pharmacokinetic data point to the liver, kidney and intestines as the key target organs involved in metabolization. Metformin reduces liver production of glucose, decreases its intestinal absorption and enhances insulin sensitivity by increasing both peripheral glucose uptake and utilization [2].

Metformin has a plasmatic peak at two hours post-ingestion and has a half-life of around 2.5-5 hours. Up to 90% of the drug is urinary excreted in 12 hours [3].

Ingested metformin is taken into hepatocytes by the organic cation transporter-1 (OCT1). As it is positively charged, it accumulates in the mitochondria inhibiting complex I of the respiratory chain, thus suppressing ATP production. This determines an increase in cytoplasmic ADP:ATP and AMP:ATP ratios, mirroring an imbalance in

cellular energy homeostasis. Therefore AMP-activated protein kinase (AMPK), which plays a key role in glucose metabolism regulation essays to reset the balance by activating catabolic mechanisms that generate ATP while switching off cellular processes that consume it [4]. AMPK can be activated through lysosomal mechanism, apart from mitochondrial and it also phosphorylates two isoforms of acetyl-CoA carboxylase, inhibiting fat synthesis, activating fat oxidation and enhancing insulin sensitivity. Increase in AMP:ATP ratio also determines inhibition of fructose-1,6-bisphosphatase enzyme, inhibiting the gluconeogenesis. AMP might independently reduce expression of gluconeogenic enzymes by lowering cAMP used for cell signaling [5]. Metformin also inhibits glycerol-3-phosphate dehydrogenase in mitochondria, which induces suppression of gluconeogenesis, including conversion of lactate to pyruvate [6].

It appears that the liver may not be as important for metformin action as it was initially thought. The gut also has a significant role in the blood glucose lowering effect of metformin by changing the glucose uptake and anaerobic metabolism, increasing production of glucagon-like peptide-1 (GLP-1) and alteration of intestinal microbiome [7], [8].

Metformin is eliminated mostly by the kidneys. Its clearance is about 10 times higher than creatinine clearance, hence factors that decrease kidney function, such as chronic kidney disease, acute kidney injury, dehydration, age can increase metformin levels. Metformin should be avoided in patients with altered renal function (eGFR <60 mL/min) or dose should be adjusted accordingly [9].

Metformin has a good safety profile with few adverse reactions, most of which are transient and usually associated with rapid titration and high-dose initiation of metformin [10]. Therapeutic drug levels are situated at 0.5 - 2 mg/L [11]. Metformin intoxication can be responsible for lactic acidosis which represents a rare complication with an incidence of 3-4 cases per 100,000 patient years. It can be fatal in up to half of cases [12].

Metformin toxicity is usually defined by a plasma level higher than 5mcg/ml and it can occur if renal disfunction is present, in altered hepatic metabolism or in drug overdose. The majority of cases of metformin intoxication are accompanied by lactic acidosis, however few case reports with normal lactatemia were described in published literature [13].

CASE PRESENTATION

A 90-year-old female patient was admitted to the Orthopedic Department after suffering a left femoral neck fracture and left displaced distal radial epiphysis fracture. Her medical history revealed being hypertensive and had atrial fibrillation for which she had priory received no anticoagulants. Patient also suffered from type II diabetes treated with metformin, sitagliptin and gliquidone.

The patient undergoes left hip hemiarthroplasty with Austin Moore prosthesis and greater trochanter osteosynthesis with plate and screws under spinal anesthesia. Antibiotic prophylaxis was administered one hour prior to intervention and the patient was mildly sedated with intravenous Midazolam and Fentanyl. The patient is stable throughout the surgical procedure, with a mean arterial pressure of over 65mmHg, stable heart rhythm of 80-100 beats per minute and present diuresis. Intraoperative estimated blood loss was estimated at 800 mL and the patient received a unit of packed red cells.

Patient was transported in the postoperative care unit for continuous monitoring, anticoagulant therapy with low molecular weight heparin, antibiotic prophylaxis, stress ulcer prophylaxis, pain management therapy and indication to resume personal medication 24 hours after surgery.

Three days after surgical intervention, the patient is suspected for upper gastrointestinal bleeding because of melena and hematemesis. The clinical evaluation identified an altered mental state, patient was disoriented and asthenic. Skin was pale and dehydrated with minimal peripheral edema, afebrile. Respiratory frequency was about 20 breaths per minute and oxygen saturation was 96%. Blood pressure measured 136/80 mmHg with a mean ventricular rate of 86bpm.

Laboratory tests revealed significant leukocytosis with neutrophilia and lymphopenia, moderate anemia (8.9 g/dL), with a blood sugar level of 127mg/dL. Patient exhibited marked

prolongation of coagulation markers, with an INR of 7.1.

Abdominal ultrasound did not expose significant findings. Upper gastrointestinal endoscopy was recommended after an INR value drop below 2.

Meanwhile, the first blood gas analysis showed metabolic acidosis with high anion gap and hypocapnia, without hyperlactatemia (pH 7.1, pCO2 15 mmHg HCO3 10.4 mmol/L, BE 19.9 mmol/L, gap anion 29.2 mmol/L and a lactate of 1.54 mmol/L).

A metformin level ordered came back as high as 3.9 mcg/mL.

Considering the clinical and paraclinical findings, prompt interruption of metformin was performed and intravenous 8.4% sodium bicarbonate (1-2 mEq/kg body weight) was added to correct the metabolic imbalance. Calcium gluconate 9.4 % was also supplemented. Pausing anticoagulant administration along with administration of plasma units, vitamin K and fibrinogen for correcting coagulation markers and high dose of proton-pump-inhibitor. Insulin in continuous infusion was helpful for normalizing glycemic value. Urine was collected for toxicological examination to investigate eventual causes of high anion gap metabolic acidosis, but eventually came back negative for opioids, benzodiazepines, tricyclic antidepressants, barbituric, also excluding alcohol and salicylate ingestion.

After administering sodium bicarbonate, pH value raised to 7.52, HCO3 19,2 mmol/L, BE 6,4 mmol/L and lactate level was 1.96 mmol/L.

Liver function tests showed normal transaminase and bilirubin levels, hypoproteinemia (5.5 g/dL) with hypoalbuminemia (2.06 g/dl). Elevated blood sugar levels were recorded (210mg/dL). Renal function was moderately altered, with a creatinine clearance of 41/mL/min/1.73 m^2.

Arterial blood gas after 12 hours showed a pH level of 7.50 with HCO3 of 15.1 mmol/L and lactate of 1.65 mmol/L.

DISCUSSIONS

The presented case displays a metformin-associated lactic acidosis (MALA) without hyperlactatemia.

Lactic acidosis associated with metformin usually has a progressive onset in chronically-treated patients who associate liver or renal dysfunction, due to drug decreased elimination. In rare cases, metabolic complications can install abruptly in metformin overdose [14]. Clinical symptoms include nausea, abdominal pain, hypotension and tachycardia but if acute intoxication occurs it can lead to cardiovascular collapse and hepatic dysfunction [15].

Lactic acidosis provoked by metformin occurs through inhibition of gluconeogenesis by interrupting the action of pyruvate carboxylase responsible for the conversion of pyruvate to oxaloacetate, allowing building up lactic acid [16]. Moreover, the class of biguanides lowers lactate's hepatic metabolization which can in turn increase its levels [17].

Regarding the significant metabolic imbalance, it is mandatory to analyze the causes of high anion gap metabolic acidosis, namely drug-induced or by renal failure [18].

Drug intake like glycol, methanol and aspirin were excluded as well as paracetamol overdose since administration was strictly monitored. Patient had no majorly nephrotoxic drugs during her hospital stay.

Glycemic values were maintained below 250 mg/dL, excluding the ketoacidosis hypothesis.

Since liver function tests were normal in our patient, hepatic dysfunction was ruled out as potential cause for lactic acidosis.

In patients with impaired renal function, metformin can be responsible for inducing lactic acidosis, depending on the dose and timely intervention. Actual data suggest that metformin administration is contraindicated at creatinine clearance <30 ml/min/1.73 m^2. Moreover, for creatinine clearance between 30-45 ml/min/1.73 m^2, dose adjusting is recommended [3,13,14].

The patient in the case report had a moderately decreased creatinine clearance (41 ml/min/1.73 m^2) with serum creatinine value of 1.22 mg/dL [19].

There are certain situations that might precipitate the apparition of metabolic acidosis associated to metformin administration, such as acute renal dysfunctions secondary to dehydration, gastrointestinal manifestations

(diarrhea, vomiting), surgical stress, especially in elderly patients with decreased eRFG [20].

As such, if administered in therapeutic doses, metformin might induce lactic acidosis if associated comorbidities are present such as tissue hypoperfusion, infections or sepsis, heart of liver failure. The latter are all risk factors for lactic acidosis themselves [21].

The presented patient underwent major orthopedic procedure, with surgical stress adding to her already impaired renal function and thus making it difficult for metformin to excrete properly.

Hemodialysis is a viable strategy in toxicity induced by metformin overuse since most of the drug is removed through the urine. However, because of significant distribution volume, it cannot eliminate large drug quantities, but it can improve the severity of acidosis [22].

Most cases presented in the literature regarding metformin intoxication associate lactic acidosis. However, the feature of the presented case was that lactate levels were repeatedly normal. Serum lactate-maintained values under 2 mmol/L throughout the investigation.

The absence of hyperlacticaemia can be explained by recognition of the cause of lactic acidosis and early administration of intravenous bicarbonate before lactate plasma levels could increase significantly.

A systematic literature review published by Dell'Aglio et al in 2009 aimed to establish the link between mortality and serum pH, lactate levels and metformin concentrations in acute metformin overdose. Ten articles were included, and results suggested that the more profound the acidemia and the higher lactate serum lactate and drug levels, the higher the risk of death in exposed patients. No patient in the analysis died if pH was more than 6.9, lactate level was less than 25 mmol/L, or metformin concentration was less than 50 μg/mL [23].

As the case of our patient, the lack of major laboratory disturbances and their rapid correction made it possible to avoid death.

CONCLUSIONS

Metformin- induced metabolic acidosis is a potentially life-threatening condition. The present case report aims at raising awareness throughout physicians to early recognize signs of drug induced lactic acidosis and avoid preventable situations. Thus, discontinuation of metformin is mandatory in patients prone to dehydration or aggravating renal failure, especially when associated with nephrotoxic drugs.

Prompt intervention is needed if MALA is suspected with supportive treatment and hemofiltration to eliminate drug to improve patients' outcome and avoid multi-organ failure.

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