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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Early initiation of continuous renal replacement therapy for metformin-associated lactic acidosis

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SUMMARY

Introduction Rapid diagnosis of metformin-associated lactic acidosis (MALA) and initiation of continuous renal replacement therapy (CRRT) in diabetic patient successfully corrects a severe metabolic disorder of a patient with acute renal failure.

Case outline A 58-year-old male patient with a medical history of type 2 diabetes and alcohol abuse was admitted to the Emergency Department because of vomiting, diarrhea, and altered mental status. Initial arterial blood gas analysis revealed severe metabolic acidosis (pH: 6.8, $PaCO_2$: 12 mmHg, HCO_3: 3.2 mmol/l), but the lactate level was too high to measure. MALA was suspected based on progressive lactic acidosis and past intake of metformin. Renal replacement therapy was initiated – continuous veno–venous hemodiafiltration, and as a result a significant improvement of the clinical status, with both blood pH and lactate level showing normalization, was achieved after finishing CRRT.

Conclusion MALA carries an ominous prognosis. This case suggests early initiation of CRRT in hemodynamically unstable diabetic patients with MALA.

Keywords: MALA; acute kidney injury; dialysis; lactic acidosis

INTRODUCTION

Metformin-associated lactic acidosis (MALA) is a rare complication of metformin treatment of type 2 diabetes, which can be caused due to a large intake amount of the drug, or it can be provoked by comorbidities such as renal or hepatic insufficiency or acute infection. Clinically, MALA can be presented with gastrointestinal symptoms (nausea, vomiting, and diarrhea), altered mental status, hypotension, and hypothermia [1]. In patients with hemodynamic instability due to septic shock and MALA, continuous renal replacement therapy (CRRT) has been reported to be successful.

CASE REPORT

A 58-year-old male patient with a medical history of type 2 diabetes and alcohol abuse was admitted to the Emergency Department due to vomiting, diarrhea, and altered mental status, with a Glasgow coma score of 8, Acute Physiology and Chronic Health Evaluation II score of 29, and the Sequential Organ Failure Assessment score of 8. The patient was tachypneic (27 breaths/min.), tachycardic (118 beats/min.), hypotensive (60/30 mmHg), oliguric (diuresis 400 ml). Initial arterial blood gas (ABG) analysis revealed severe metabolic acidosis (pH: 6.8, $PaCO_2$: 12 mmHg, HCO_3: 3.2 mmol/L), but the lactate level was too high to measure. Other initial laboratory results are presented in Table 1. Due to altered mental status and hypovolemic shock, failing to respond to large volume of intravenous fluids, the patient was intubated, mechanical lung ventilation was started in combination with vasoactive support (dopamine/norepinephrine). Empirical parenteral antibiotic therapy was introduced (ceftriaxone/levofloxacin), based on the kidney function. He was given intravenous sodium bicarbonate, and ABG analysis repeated after an hour showed pH of 6.9, with bicarbonate of 4.6 mmol/L, lactate level being 24.8 mmol/L. Electrocardiogram, abdominal ultrasonography and cranial computed tomography scan showed no remarkable findings. The chest X-ray revealed bilateral paracardial areas of lung inflammation (Figure 1). MALA was suspected based on progressive lactic acidosis and past intake of metformin. Serum metformin concentration was 571 umol/L (reference range > 5 ug/ml). After intubation, a nephrologist and an anesthesiologist were consulted, the double lumen catheter was inserted in the right internal jugular vein, and renal replacement therapy (RRT) was initiated – continuous veno–venous hemodiafiltration

Table 1. Initial laboratory results

Blood glucose level (mmol/l)	18.1
Blood urea nitrogen (mmol/l)	35.2
Serum creatinine (μmol/l)	1158
Potassium (K+) (mmol/l)	6.8
C-reactive protein (mg/ml)	61
Procalcitonin (ng/ml)	6.11

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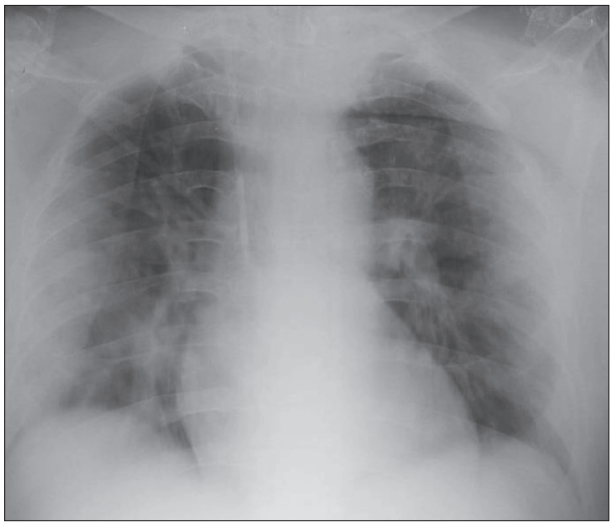

Figure 1. Chest X-ray with bilateral areas of lung inflammation

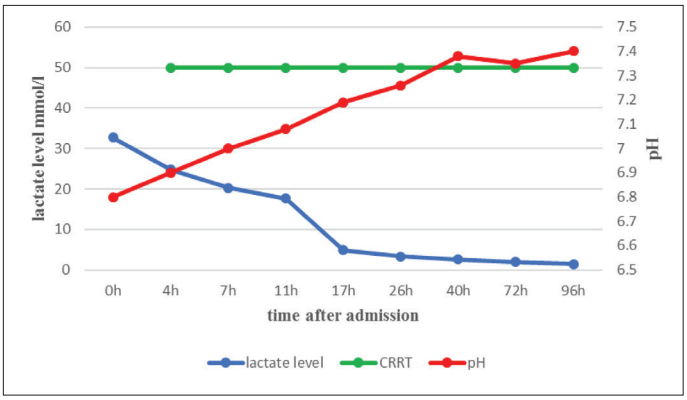

Figure 2. Improvement of blood pH and lactate level during continuous renal replacement therapy (CRRT)

with the oXiris adsorbing membrane (Baxter International Inc., Deerfield, IL, USA), through a Prismaflex CRRT set (Baxter International Inc.). Blood flow rate was 150 ml/min. The therapeutic dosage was 30 ml/kg/h. For anticoagulation, unfractionated heparin was utilized. After the first 24 hours of CRRT, pH improved to 7.179, with an ABG lactate of 21.72 mmol/L. Significant improvement of the clinical status, with both blood pH and lactate level showing normalization, was achieved after finishing one session of CRRT, which lasted 96 hours (Figure 2). Consequently, serum metformin concentration decreased to 104 umol/L. Vasoactive support was reduced on the second day after starting the CRRT, and was discontinued on the fifth day. Hourly diuresis was initially 10–15 ml/h, and during the CRRT it started increasing, so at the end of the procedure the patient had diuresis of 1700 ml/24h. The patient was extubated on day 5 and transferred to the Nephrology Clinic, where from he was discharged (blood urea nitrogen: 10.3; creatinine: 151 umol/L; pH 7.38; pCO_2: 38 mmHg; pO_2: 90 mmHg; lactate level: 0.7 mmol/l; base excess: 3.8; HCO_3 25.1, diuresis: 2200 ml/24 h).

This case report was approved by the Ethics Committee of the University Clinical Centre of Vojvodina.

DISSCUSION

Metformin is a biguanide antihyperglycemic drug, which is used as a first-line agent to treat type 2 diabetes. It inhibits the conversion of lactate to pyruvate; this results in both lactate production and its impaired metabolism. Lactic acidosis is a rare but serious adverse effect in metformin-treated patients. The incidence of MALA is mostly reported to occur in 0.03–0.1 cases per 1000 patient-years but has a high mortality rate, reported to be around 50% [2]. CRRT and sustained low-efficacy dialysis for the treatment of MALA have been documented in some case reports [3, 4].

MALA is generally treated with supportive therapy, including RRT. Applying RRT in patients with MALA, significant base deficit can be corrected; it also directly effects extracellular fluid volume and serum osmolality [5]. With regard to RRT for MALA treatment, a recent study revealed that the clearance of metformin by continuous veno–venous hemofiltration was less than that generally reported to occur with conventional hemodialysis. Thus, continuous veno–venous hemofiltration should be considered only in patients who are too hemodynamically unstable to tolerate hemodialysis. Indications for extracorporeal treatment include lactate > 20 mmol/L, pH 7.0, shock, failure of standard supportive measures, and a decreased level of consciousness [6].

In our case, CRRT was applied because the lactic acidosis was caused by metformin accumulation in the setting of acute kidney injury, gastroenteritis, and subsequent hypovolemic shock. In our patient, cardiorenal syndrome was interpreted as a prerenal deterioration of renal function due to systemic hypoperfusion with consecutive inflammatory changes in the lungs [7].

In a retrospective analysis by Mariano et al. [8], survival rate with CRRT in patients with MALA was noted to be 80%.

The clearance of drugs by CRRT may be less effective than by intermittent hemodialysis, but needs to be considered for patients who are hemodynamically unstable. In our patient, intermittent dialysis was difficult because the patient was hemodynamically unstable receiving high doses of vasopressors. After CRRT was initiated, his lactate level and pH value improved and he subsequently recovered from shock. CRRT is an effective treatment for MALA if intermittent hemodialysis cannot be performed due to hemodynamic instability. Also, one of many advantages of the CRRT is the removal of substances that can produce severe metabolic acidosis, such as alcohol, whose abuse was noted in medical history of our patient, proven by Jha and Padmaprakash [9]. In our case, the use of continuous veno–venous hemodiafiltration in the setting of hemodynamic instability led to a rapid correction of metabolic disorders and hemodynamic stabilization, and, ultimately, to recovery.

Acute MALA carries an ominous prognosis. This case suggests the application of early initiation of CRRT in hemodynamically unstable diabetic patients with MALA.

Conflict of interest: None declared.

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Рана примена континуиране терапије замене бубрежне функције код лактатне ацидозе узроковане метформином

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САЖЕТАК

Увод Правовремена дијагноза лактатне ацидозе узроковане метформином и започињање континуиране терапије замене бубрежне функције код дијабетесних болесника са акутном бубрежном инсуфицијенцијом успешно коригује тешки метаболички поремећај.

Приказ болесника Болесник старости 58 година, са коморбидитетима у виду дијабетесне болести типа 2 и алкохолизма, хоспитализован је у Одељењу ургентне интерне медицине због повраћања, дијареје и измењеног стања свести. Иницијалне артеријске гасне анализе крви показале су тешку метаболичку ацидозу (*pH*: 6.8, $PaCO_2$: 12 *mmHg*, HCO_3: 3.2 *mmol/l*), а ниво лактата је био превисок да би се измерио. Посумњано је да се ради о лактатној ацидози узрокованој метформином, с обзиром на тешку лактатну ацидозу и податке о узимању метформина. Започета је терапија замене бубрежне функције – континуирана вено–венска хемодијафилтрација, и као резултат постигнуто је значајно побољшање клиничког стања болесника, уз нормализацију вредности *pH* и нивоа лактата.

Закључак Акутна лактатна ацидоза узрокована метформином може имати неповољну прогнозу. Овај приказ предлаже разматрање раног започињања континуиране терапије замене бубрежне функције код хемодинамски нестабилних болесника са лактатном ацидозом узрокованом метформином.

Кључне речи: лактатна ацидоза узрокована метформином; акутно оштећење бубрега; дијализа; лактатна ацидоза