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Case Report / Приказ болесника

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

Рана примена континуиране замене бубрежне функције код лактатне ацидозе узроковане метформином

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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 Emergency department because of the vomiting, diarrhea and altered mental status. 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. MALA was suspected based on progressive lactic acidosis and past intake of metformin. The renal replacement therapy (RRT) was initiated- continuous veno–venous hemodiafiltration (CVVHDF), 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 Acute metformin-associated lactic acidosis carries an ominous prognosis. This case suggests the application of early initiation of CRRT in hemodynamically unstable diabetic patients with MALA.

Keywords: MALA; AKI; dialysis; lactic acidosis

САЖЕТАК

Увод Правовремена дијагноза метформин-удружене лактатне ацидозе (*MALA*) и започињање континуиране замене бубрежне функције (*CRRT*) код дијабетесних болесника са акутном бубрежном инсуфицијенцијом успешно коригује тешки метаболички поремећај.

Приказ болесника Болесник старости 58 година, са коморбидитетима у виду дијабетесне болести тип 2 и алкохолизма, хоспитализован је у Одељење 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 *MALA*, с обзиром на тешку лактатну ацидозу и податке о узимању метформина. Терапија замене бубрежне функције је започета – континуирана вено-венска хемодијафилтрација (*CVVHDF*), и као резултат дошло је до значајног побољшања клиничког стања болесника, уз нормализацију вредности *pH* и нивоа лактата.

Закључак Акутна метформин-удружена лактатна ацидоза може имати неповољну прогнозу. Овај приказ предлаже разматрање раног започињања *CRRT* код хемодинамски нестабилних болесника са *MALA*.

Кључне речи: *MALA*; *AKI*; дијализа; лактатна ацидоза

INTRODUCTION

Metformin-associated lactic acidosis is a rare complication of metformin treatment of type 2 diabetes, which can be caused due to take in large amount of the drug, or it can be provoked 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 Emergency department because of the vomiting, diarrhea and altered mental status. Glasgow coma score 8, Acute Physiology and Chronic Health Evaluation II score 29, Sequential Organ Failure Assessment score 8. The patient was tachypneic (27/min), tachycardic (118/min), hypotensive (60/30mmHg), oliguric (diuresis 400ml). 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 (dopamin/norepinephrine). Empirical parenteral antibiotic therapy was introduced (cephtriaksone/levofloksacin), based on the kidney function. He was given intravenous sodium bicarbonate, and repeated ABG after an hour showed pH of 6.9 with bicarbonate of 4.6 mmol/L, lactate level 24.8mmol/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 571umol/l (reference range >5ug/ml). After intubation, nephrologyst and anesthesiologyst were consulted, the double lumen cathether was inserted in the right internal jugular vein and the renal replacement therapy (RRT) was initiated- continous veno-venous haemodiafiltration (CVVHDF) with the adsorbing membrane oXiris (Baxter, IL, USA), through a Prismaflex CRRT set (Baxter, IL, USA). Blood flow rate was 150ml/min. The therapeutic dosage was 30ml/kg/h. For anticoagulation, unfractioned heparin was utilized. After the first 24h CRRT, pH improved to 7.179 with ABG lactate of 21.72 mmol/l. Significant improvement of the clinical status, with both blood pH and lactate level showing normalisation was achieved after finishing one session of TCRRT, which lasted for 96h (Figure 2). Consequently, serum metformin concentration decreased to 104 umol/L**.** Vasoactive support was reduced on the 2nd day after starting the CRRT, and it was discontinued on the 5th day. Hourly diuresis was at first 10-15ml/h, and during the CRRT it started increasing, so at the end of the procedure the patient had diuresis 1700ml/24h. The patient was extubated on day 5 and transferred to the Nephrology clinic, where from he was discharched (BUN 10,3, creatinine 151 umol/l, pH 7,38, pCO2 38mmHg, pO2 90mmHg, lac level 0,7mmol/l, BE 3,8, HCO3 25,1, diuresis of 2200ml/24h).

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]. Continuous renal replacement therapy (CRRT) and sustained low-efficacy dialysis (SLED) 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, and also it directly effects extracellular fluid volume and serum osmolality [5]. With regard to renal replacement therapy 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., survival rate with CRRT in patients with MALA was noted to be 80% [8].

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 et al [9]. In our case, applying of CVVHDF in the setting of hemodynamic instability, led to rapid correction of metabolic disorders and hemodynamic stabilization, and, in final, to good recovery.

Acute metformin-associated lactic acidosis 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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Table 1. Initial laboratory results

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

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

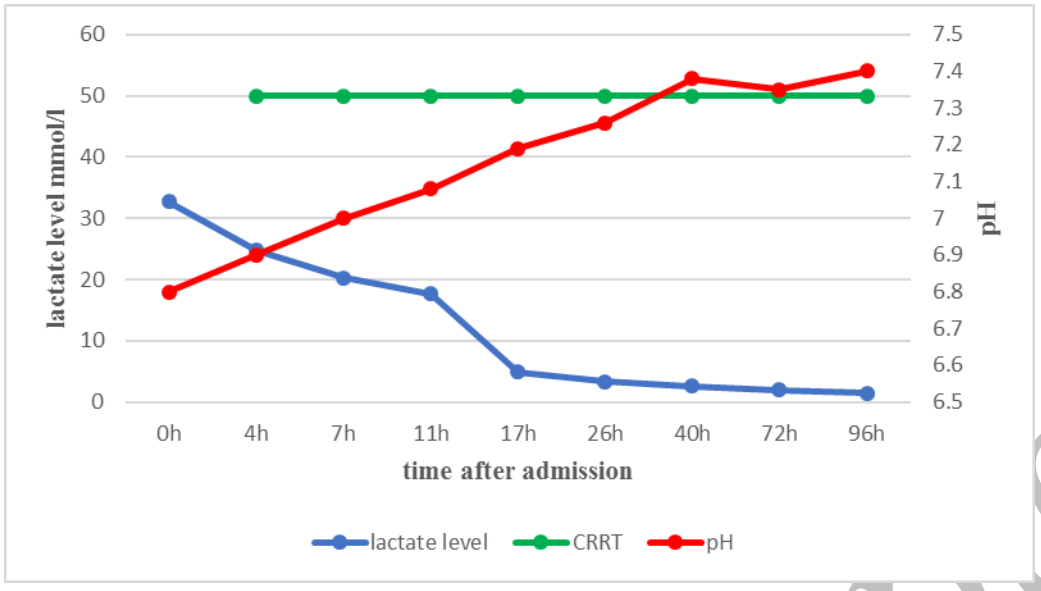

Figure 2. Improvement of blood pH and lactate level during continuous renal replacement therapy (CRRT)

