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# Citrate intoxication in muscle damage – unappreciated site of citrate metabolism in critically ill patients – case report

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## Abstract

***Background.*** Regional citrate anticoagulation (RCA) is considered a safe alternative to systemic anticoagulation during Continuous Renal Replacement Therapy (CRRT) in critically ill patients. Citrate undergoes rapid metabolism, which occurs mainly in liver, and to a lesser extent in skeletal muscle and renal cortex. Although it is well known that citrate metabolism is deranged in liver dysfunction, only few cases of citrate intoxication have been described so far. One should remember that citrate has been successfully used in liver failure patients during albumin dialysis. The role of muscles in citrate metabolism has never been appreciated. ***Cases report***. We present two cases of severe citrate intoxication during CRRT in patients with extensive muscle damage: 72-year-old male admitted to ICU with multiple trauma sustained in a road accident and 55-year-old male treated with influenza B virus and septic shock. Based on our observations, we conclude that muscle metabolism of citrate is unappreciated, especially in accompanying liver failure. *Anestezjologia i Ratownictwo 2016; 10: 299-302.*

*Keywords: citrate anticoagulation, continuous renal replacement therapy, critical care, rhabdomyolysis*

## Introduction

Regional citrate anticoagulation (RCA) has become a basic method of anticoagulation during continuous renal replacement therapy (CRRT). Citrate undergoes rapid metabolism, which occurs mainly in liver, and to a lesser extent, in skeletal muscle and renal cortex [1,2]. Impaired citrate metabolism and citrate accumulation have been described in patients with acute liver failure and during anhepatic phase of liver transplantation [1, 3-5]. On the other hand, citrate has been successfully used in liver failure patients during albumin dialysis [6,7]. We report two patients with liver dysfunction, who developed severe citrate intoxication due to coexisting muscle damage.

## Case 1.

A 72-year-old male was admitted to ICU with multiple trauma sustained in a road accident. His diagnostics revealed: subarachnoid haemorrhage, brain contusion, compressive lumbar fracture (L1), upper and lower limb fractures, liver and kidney contusion. At arrival to hospital he was conscious, but was quickly intubated due to deterioration in the neurological status. He required fluids, blood transfusion and catecholamines due to hemodynamic instability. After a few hours of stabilisation, the patient's condition started deteriorating. Acute kidney failure with high potassium (7.9 mmol/l), creatinine (3.63 mg/dl), severe metabolic acidosis (pH 6.77, HCO-39.2 mmol/l, lactate 18 mmol/l) and anuria developed. Liver enzymes were elevated (ALT 3684 IU/l, AST 5651 IU/l). The patient required CRRT and higher doses of catecholamines. CRRT was performed in CVVHDF mode with citrate. We started CRRT with a standard dose of citrate (3mmol/l) and 100% calcium chloride compensation. During treatment, ionized calcium ($iCa^{++}$) levels star-

ted to decrease and required increased compensation. Changes in iCa++ and pH and corresponding calcium compensation are presented in diagram (figure I). Despite CRRT, metabolic acidosis increased, while potassium level stayed high. Calcium substitution was ineffective, it only increased total calcium (tCa) levels. We suspected citrate intoxication and we calculated $tCa/iCa^{++}$ ratio that was 3.26. It was unexpected that INR level was only slightly higher (1.60), we concluded that liver contusion could not have been the only reason for citrate intoxication. We diagnosed severe muscle rhabdomyolysis with creatinine phosphokinase (CPK) 46242 IU/l performed after stopping citrate. The patient died of multiorgan failure (MOF) after 2 days of ICU treatment.

## Case 2.

A 55-year-old male was admitted to ER with dyspnoea, malaise and low blood pressure. Few days before arrival to ER, he had had sore throat, productive cough, joint and muscle pain, without fever. He was difficult to diagnose. At first, acute coronary syndrome was suspected, then right heart failure, aortic aneurysm and Guillain-Barre syndrome because of muscle weakness and paresis. Eventually, sepsis was diagnosed. The patient required intubation due to acute respiratory failure and muscle weakness. He was admitted to ICU. The patient required mechanical ventilation, catecholamines, broad spectrum antibiotics and fluids. Laboratory result, at admission to ICU, showed: polyglobulia (Hgb 19.7 g/dl, Hct 53.7%), leukocytosis (WBC 18.5 x $10^3$/µl), low platelet count (PLT 99 x $10^3$/µl), metabolic acidosis (pH 7.27, HCO3- 14,5 mmol/l, lactate 7.1 mmol/l, BE: -12.4 mmol/l), CPK 13059 IU/l. Inflammatory parameters were moderately deranged (CRP 15.2 mg/l, PCT 0.19 ng/ml), as well as kidney (creatinine 1.51 mg/dl, urea 47 mg/dl) and liver parameters (AST 457 IU/l, ALT 86 IU/l, INR 1.11). Because of septic shock and suspected muscle damage, CRRT was performed in CVVHDF mode with citrate. We started CRRT with a standard dose of citrate (3 mmol/l) and 100% calcium chloride compensation. During CRRT, $iCa^{++}$ started to decrease and required

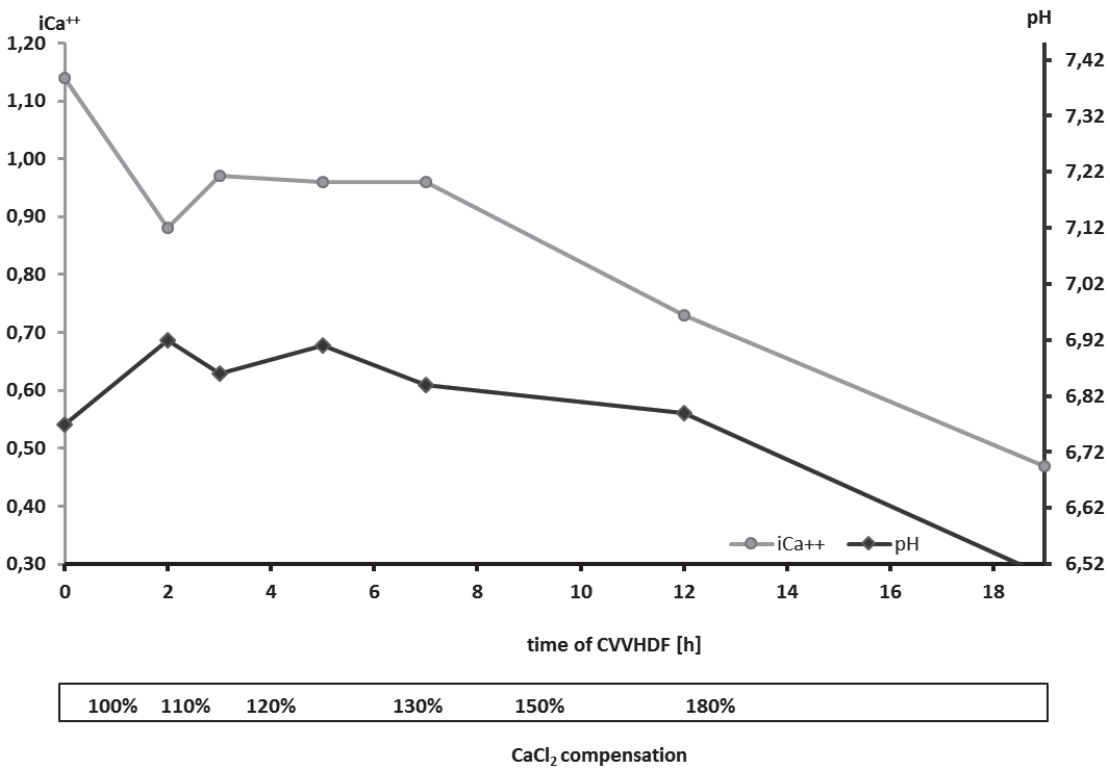


Figure I. Changes in iCa++ and pH during CVVHDF with citrate and corresponding calcium compensation

increased compensation. Changes in iCa++ and pH and corresponding calcium compensation are presented in diagram (figure II). The main clinical problem was hemodynamic instability with resistance to increased doses of catecholamines. Transthoracic echocardiography revealed severe left and right ventricular dysfunction. Hypocalcaemia was suspected as a reason for heart failure and additional ampoules of calcium chloride were infused. Heart function improved for a short period of time. The patient's condition constantly deteriorated. Laboratory test after 24h showed: severely deranged liver parameters (AST 2277 IU/l, ALT 388 IU/l), increased rhabdomyolysis (CPK 135232 IU/l), metabolic acidosis (pH 7.16, HCO3-113,5 mmol/l, lactate 4.8 mmol/l, BE -14.5 mmol/l) and hyperkaliaemia ($K^+$ 7.7 mmol/l). We diagnosed influenza B virus as a reason for septic shock. We also suspected citrate intoxication although $tCa/iCa^{++}$ was 2.46 and we stopped citrate. Ionized calcium started to increase and $tCa/iCa^{++}$ decreased to 1.77. The whole treatment was ineffective, the patient died of MOF after 2 days of ICU treatment.

## Discussion

Liver is the main route of citrate metabolism and its impairment increases risk of citrate intoxication. Deranged metabolism in Krebs cycle leads to accumulation of calcium citrate complexes in blood, which results in metabolic acidosis and ionised hypocalcaemia. Laboratory finding of citrate accumulation, frequently used in clinical practice, is the ratio between total and ionized calcium ($tCa/iCa^{++}$). > 2.5 ratio predicts citrate accumulation in critically ill patients [4]. There are few studies describing clinical consequences of citrate intoxication and resulting hypocalcaemia [3,5].

We use RCA during CRRT since 2010. During

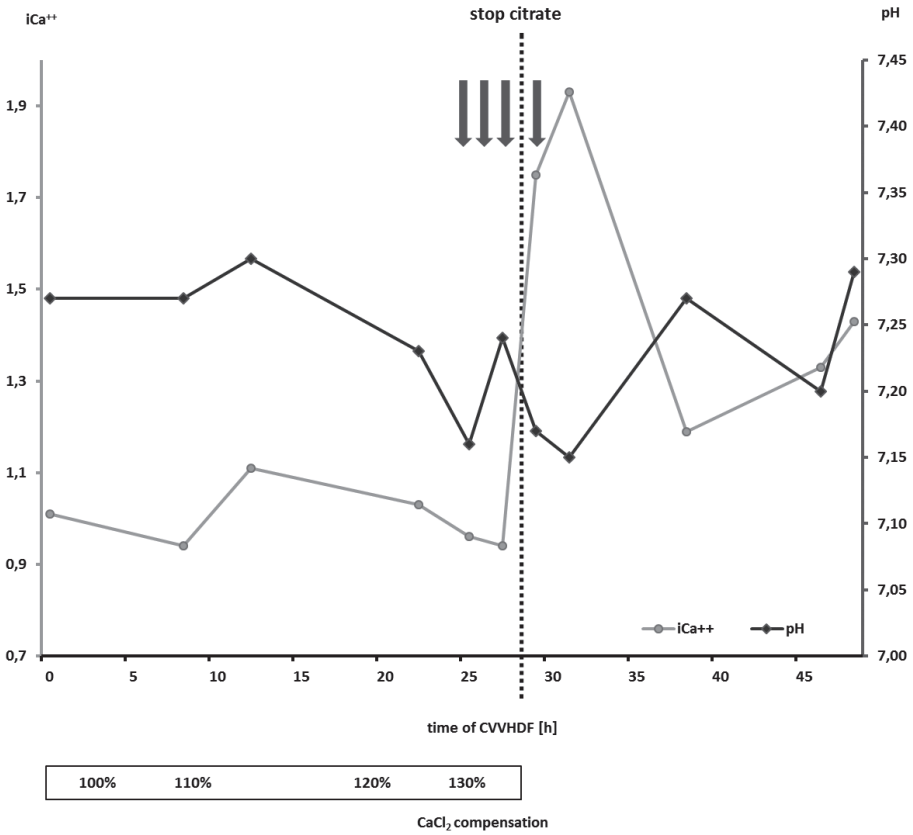


Figure II. Changes in $iCa^{++}$ and pH during CVVHDF with citrate and corresponding calcium compensation. Additional calcium chloride ampules are marked with arrows and citrate withdrawal is marked with dotted line

that period, we dialysed 222 critically ill patients and 88(40%) of them had liver dysfunction. The two presented patients are the only cases, in which we have diagnosed severe citrate intoxication.

A clinician, who performs CRRT with citrate in critically ill patients, should become concerned, when there is a constant need to increase calcium compensation on CRRT machine. Sometimes, at the start of CRRT treatment, it is not obvious that patient develops liver dysfunction or muscle damage. Unexpected ionized hypocalcaemia, metabolic acidosis and increased calcium substitution can be the first sign of liver and muscle impairment. Measuring tCA/iCa$^{++}$ ratio might be helpful but not decisive. In Case 2, the ratio was 2.46 and we decided to stop citrate because of severe circulatory failure resulting from ionized hypocalcaemia. Only additional ampules of calcium chloride resulted in temporary inotropic effect with increased stroke volume and blood pressure.

The two reported patients had different diagnosis, etiology, concomitant diseases and different indications to CRRT. What those patient had in common was extensive muscle damage confirmed by CPK. Based on our observations, we conclude that muscle metabolism of citrate is unappreciated, especially in accompanying liver failure.

**Conflict of interest**
None

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**References**

1. Kramer L, Bauer E, Joukhadar C, Strobl W, Gendo A, Madl C, et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. Crit Care Med. 2003;31(10):2450-5.
2. Wexler IB, Pincus JB, Natelson S, Lugovoy JK. III. The fate of citrate in erythroblastotic infants treated with exchange transfusion 12. J Clin Invest. 1949;28(3):474-81.
3. Marquez J, Martin D, Virji MA, Kang YG, Warty VS, Shaw B, et al. Cardiovascular depression secondary to ionic hypocalcemia during hepatic transplantation in humans. Anesthesiology. 1986;65(5):457-61.
4. Meier-Kriesche HU, Gitomer J, Finkel K, DuBose T. Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. Crit Care Med. 2001;29(4):748-52.
5. Meier-Kriesche HU, Finkel KW, Gitomer JJ, DuBose TD. Unexpected severe hypocalcemia during continuous venovenous hemodialysis with regional citrate anticoagulation. Am J Kidney Dis. 1999;33(4):e8.
6. Faybik P, Hetz H, Mitterer G, Krenn CG, Schiefer J, Funk G-C, et al. Regional citrate anticoagulation in patients with liver failure supported by a molecular adsorbent recirculating system. Crit Care Med. 2011;39(2):273-9.
7. Morgera S. Regional anticoagulation with citrate: expanding its indications. Crit Care Med. 2011;39(2):399-400.