Monitoring and safe use of regional citrate anticoagulation for renal replacement therapy in patients with metformin intoxication: a case series and mathematical model

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INTRODUCTION

Metformin intoxication causes lactic acidosis inhibiting Krebs' cycle and oxidative phosphorylation. The Extracorporeal Treatment In Poisoning group recommends Continuous Renal Replacement Therapy (CRRT) for the removal of metformin in critically ill patients. From 2012, KDIGO guidelines recommend using Regional Citrate Anticoagulation (RCA) due to its lower risk of bleeding than systemic heparin. Metformin inhibits citrate metabolism in the Krebs' cycle; therefore, the risk of citrate accumulation can be supposed with scarce evidence from the literature. We described how the physicochemical approach to acid-base could safely exclude significant citrate accumulation.

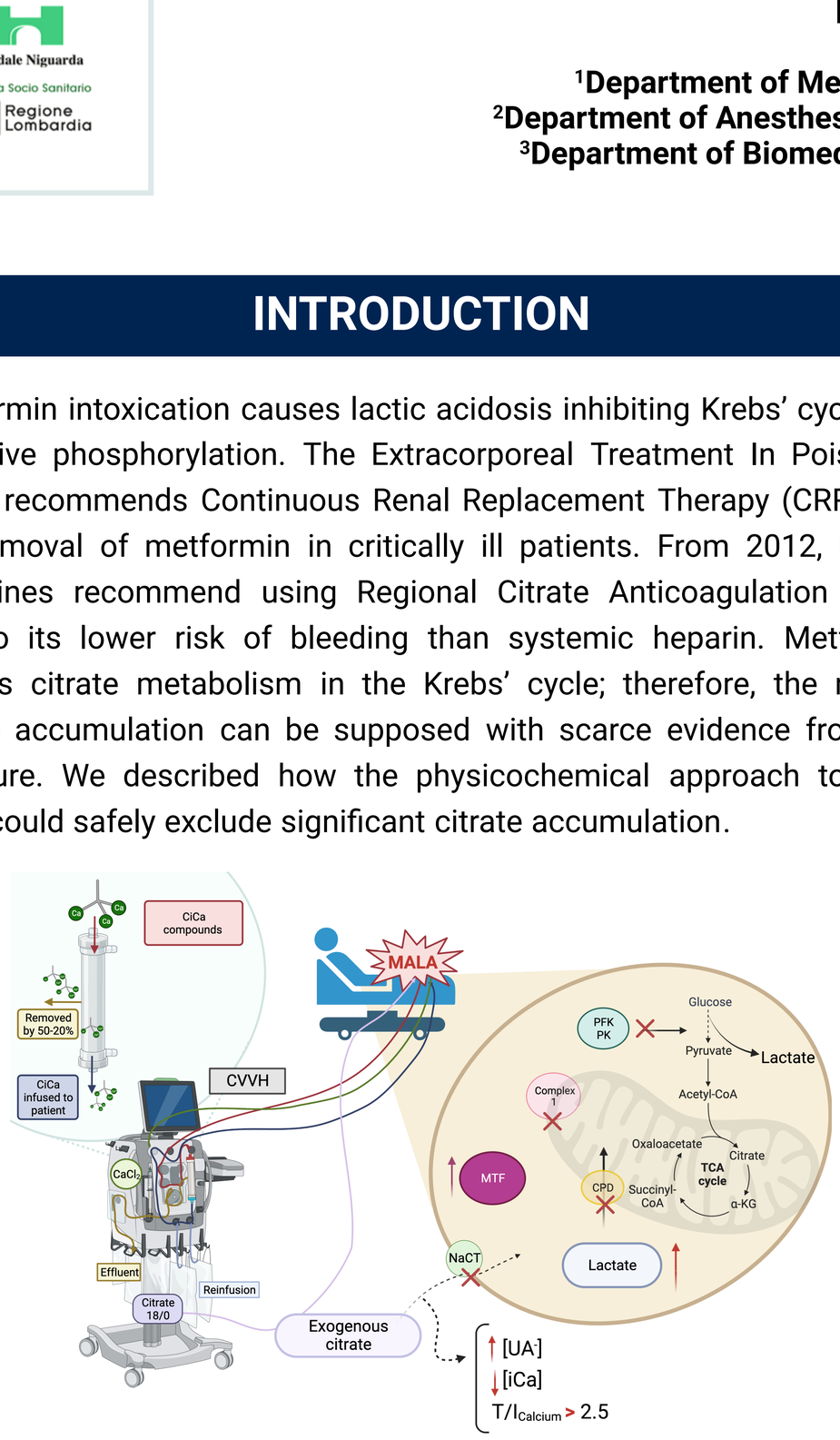

Figure 1. Possible mechanisms involved in citrate accumulation during accidental metformin intoxication.

METHODS

Three patients admitted to the Intensive Care Unit (ICU) with a diagnosis of Metformin-associated Lactic Acidosis (MALA) and treated with CRRT were studied (Table 1). A mathematical model was developed to simulate the expected citrate accumulation occurring during Continuous veno-venous hemofiltration (CVVH) set as follows: blood flow 150 ml/min, RCA with citrate of 18 mmol/L at 1500 ml/h, post-dilution replacement flow 1500 ml/h, no weight loss. The potential citrate blood accumulation was indirectly monitored as a Total-to-Ionized calcium ratio (*T/I ratio*) above 2.5 and by calculating the Strong Ion Gap (SIG) to identify an increased concentration of Unmeasured Anions (UA).

RESULTS

All three patients showed a resolution of Metformin-associated Lactic Acidosis (MALA). The SIG calculated after 48h of treatment was always below 6 mEq/L (Figure 2). In the absence of any metabolism, the estimated citrate accumulation should have been 7 mmol/L after 48 hours of CVVH, corresponding to 21 mEq/L of SIG. The *T/I ratio* was consistently lower than 2.5, and the systemic ionized calcium concentration was above 0.90 mmol/L.

Variables	Patient 1	Patient 2	Patient 3
Age (year)	66	66	71
Sex	Female	Male	Female
Weight (Kg)	70	75	75
Charlson Comorbidity Index	7	6	6
Metformin concentration (mcg/mL)	28.0	10.5	82.5
Chronic Kidney Disease	No	Yes	No
Creatinine (mg/dL)	8.1	4.1	9.0
Urea (mg/dL)	140	114	190

Table 1. Patients characteristic at Intensive Care Unit admission.

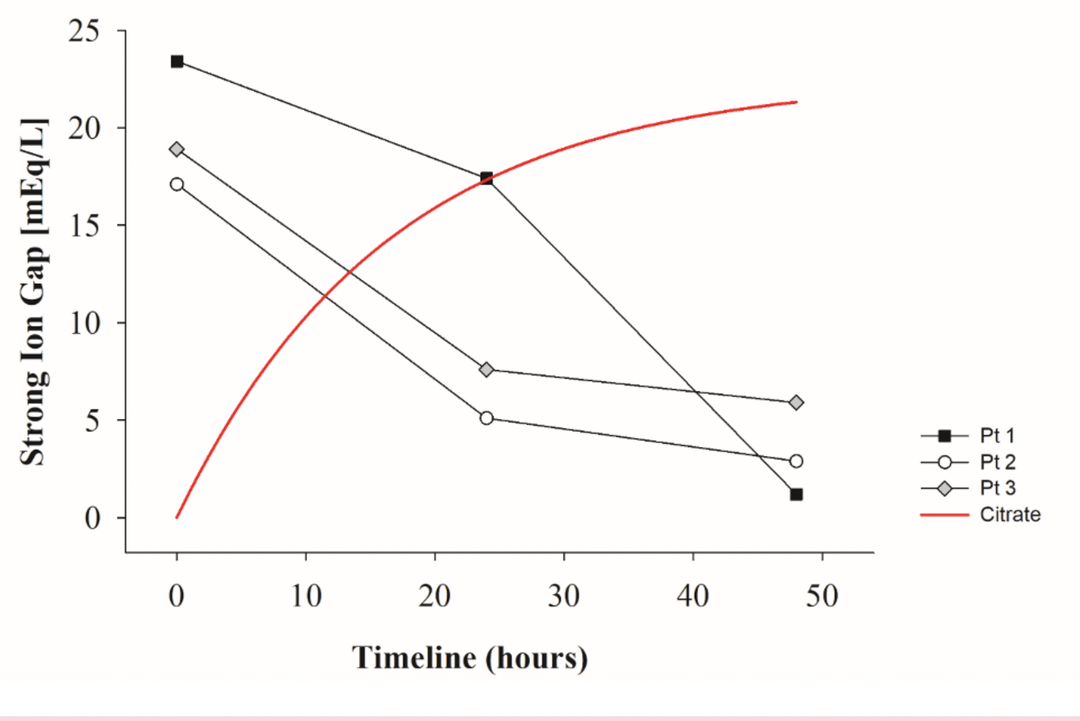

Figure 2. Strong Ion Gap in the three patients and calculated citrate accumulation with no metabolism (Red Line)

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CONCLUSIONS

In our clinical management, we used CVVH with diluted citrate solution to treat MALA patients. Our data support the safe use of diluted citrate to obtain RCA during metformin intoxication.