Citrate Pharmacokinetic Study in Decompensated Liver Disease Patients Receiving Continuous Renal Replacement Therapy

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Background

Currently, regional citrate anticoagulation (RCA) is recommended as the first line anticoagulant by Kidney Disease Improving Global Outcomes. However, little is known for the pharmacokinetic of citrate, which mainly is metabolized by liver, in the setting of decompensated liver disease. Thus, we aimed to study the citrate pharmacokinetic in decompensated liver disease patients who need continuous renal replacement therapy (CRRT).

Methods

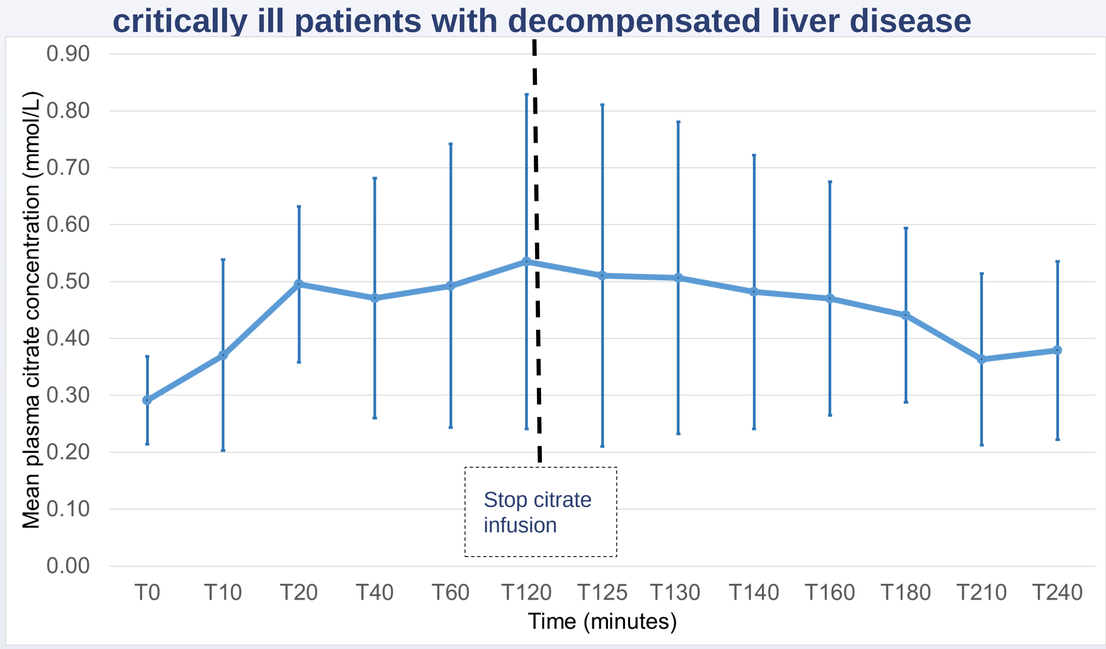
We prospectively enrolled decompensated liver disease patients receiving CRRT in intensive care unit at Chulalongkorn Hospital, Bangkok, Thailand. We used blood flow rate of 110 ml/min and pre blood pump citrate replacement fluid was infused at a final citrate concentration of 3 mmol per liter of blood flow. We infused citrate for 2 hours and serial blood sample were obtained from arterial line from baseline until 2 hours after citrate was stopped. The filter clearance was calculated using plasma concentrations of citrate at the inlet and the outlet of the filter. The body citrate clearance was defined as subtracting total citrate clearance by filter clearance. Pharmacokinetic analysis was performed with Phoenix® WinNonlin® version 8.2 (Certara USA, Inc., Princeton, NJ).

Results

There were six decompensated liver disease patients in this study. Average age were 59 years, with mean APACHE scores of 20. Clinical diagnosis were sepsis in five patients and acute heart failure in one patient. Cause of liver failure in all patients was ischemic hepatitis and two patients had underlying cirrhosis. All patients had grade 3 or more hepatic encephalopathy with mean total bilirubin of 13.94 ± 7.4 mg/dL. **Figure 1** showed systemic citrate concentration during study.

Data of citrate pharmacokinetics were shown in **Table1.** Average delivered citrate doses were 19.95 mmol/h. Mean body citrate clearance were 135.4 ± 70.5 ml/min. There were decreased body citrate clearance when compared with previous study in non-liver disease critically ill patients (648 ± 347 ml/min). Mean peak concentration of citrate was 0.64 ± 0.25 mmol/L. **Figure 2** showed concentrations of ionized calcium and magnesium during study. There were two patients with serum total calcium to ionized calcium ratio more than 2.5. However, there was no major metabolic complication of citrate. One patient experienced mild hypocalcemia.

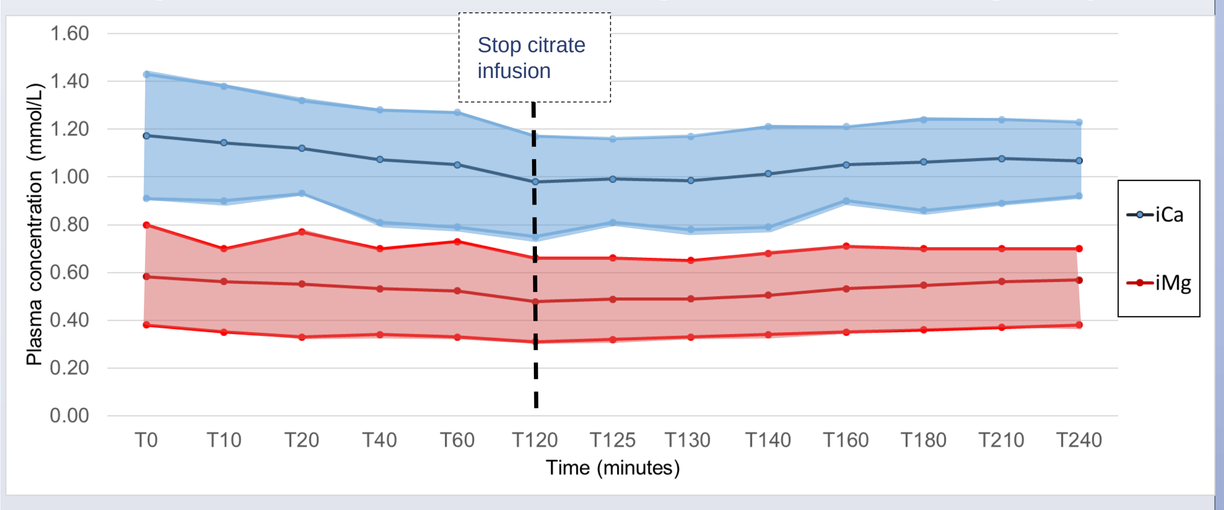
Figure 1 : Citrate concentrations during study in critically ill patients with decompensated liver disease



Data were represented with mean ± SD

Dash line represented point of stopping citrate administration

Figure 2 : Ionized calcium and magnesium levels during study



The thick blue and red lines represent mean ionized calcium and ionized magnesium levels respectively. The highlighted areas showed maximum and minimum concentrations of ionized calcium and ionized magnesium.

Dash line represent point of stopping citrate administration

Abbreviations: iCa, ionized calcium; iMg, ionized magnesium

Table 1: Citrate pharmacokinetics

	Decompensated liver disease patients	Critically ill patients with AKI*	Healthy patients*
AUC_{0-t} (mmol*min/L)	109.2 ±50.1	79.7 ±95.5	69.9 ±66.6
AUC_{0-inf} (mmol*min/L)	435.1 ±444.4	86.8 ±113.8	87.5 ±95.5
T_{max} (min)	91.7 ±61.5	110.0 ±18.1	106.6 ±21.7
Vd (L)	48.2 ±31.2	21.0 ±19.5	50.6 ±21.7
Cl_{body}(ml/min)	135.4 ±70.5	648.0 ±347.0	686.6 ±353.6
$C_{baseline}$(mmol/L)	0.29 ±0.08	0.01 ±0.13	0.02 ±0.04
C_{max}(mmol/L)	0.64 ±0.25	0.62 ±0.46	0.56 ±0.45
Total dose (mmol)	39.9	63.7 ±9.1	57.1 ±10.5

*Data from Zheng et al. (2013) PLoS ONE 8(6): e65992.;https://doi:10.1371/journal.pone.0065992

All data were shown as mean ±SD

Abbreviations: AUC, area under the curve; Vd , volume of distribution; Cl_{body}, citrate clearance of body; $C_{baseline}$, citrate concentration at baseline; C_{max}, max citrate concentration

Conclusion

This is the first pharmacokinetic study to demonstrate citrate clearance in acute decompensated liver disease receiving CRRT and showed significant reduction in citrate clearance in this specific setting. Although no major metabolic complication was observed, the use RCA in these patients must be with caution.

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