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Citrate kinetics in septic shock patients with liver dysfunction during continuous venovenous hemodiafiltration

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Background

Citrate anticoagulation is an effective alternative anticoagulant to heparin that is gaining popularity in renal replacement therapies (RRT) for critically-ill patients (1,2). Citrate is primarily metabolized by the liver (3) and in cirrhotic patients the decreased clearance can lead to accumulation and to the well known complications associated to citrate toxicity (4).

Objectives

In order to study whether citrate accumulates in septic shock patients with liver impairment, we determined citrate in plasma and dialysate during continuous veno-venous hemodiafiltration (CVVHDF).

Tab 1: Clinical data of patients at beginning of CVVHDF

Pts n.	Age/Sex Years	Diagnosis	CVVHDF days/filters	NA/DA* µg/Kg/min	AST/ALT UI/L	Bilirubin mg/dl	Exitus
1	65/M	Burns 25%	1/1	0.60/3.0	85/48	3.8	Yes
2	77/F	Burns 35%	2/3	0.30/3.0	69/52	4.0	Yes
3	78/F	Burns 18%	4/2	0.00/5.0	24/14	1.3	Yes
4	62/M	Burns 18%	5/4	0.00/8.0	11/11	2.1	No
5	78/F	Burns 15%	1/1	0.50/10	29/13	2.6	Yes
6	81/M	Polytrauma	10/6	0.20/6.0	31/41	7.8	Yes
7	49/M	Polytrauma	7/3	0.25/5.0	239/37	35.0	Yes
8	67/M	Fasciitis	3/5	0.00/5.0	120/78	1.6	No
9	53/M	Peritonitis	2/1	0.00/5.0	35/41	2.1	No
10	28/M	Polytrauma	3/1	0.00/7.0	1443/295	2.2	No
11	67/M	Burns 35%	3/1	0.10/7.0	13/14	2.5	Yes
12	46/M	Burns 90%	5/2	0.70/8.0	46/25	2.1	Yes
			37/30	0.15/5.5	41/39	2.35	8/12

*NA/DA = norepinephrine / dopamine,
Values are given as median.

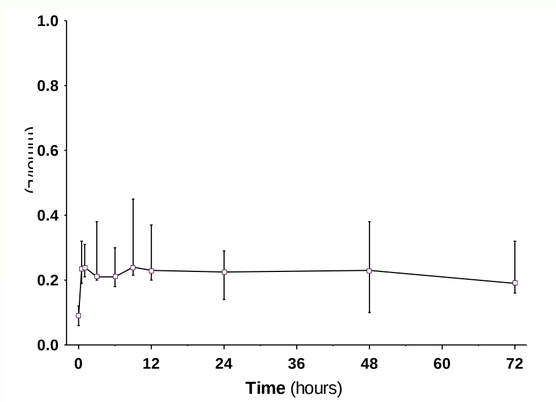

Fig 1: Citrate systemic levels during CVVHDF

Methods

An automated routine determination of citrate in plasma and dialysate was set up by adapting a commercial kit (citrate lyase method)(5). This method, intended for analysis of citrate in foodstuffs and other materials, was adapted for use in plasma by lowering the sample volume. This adaptation allowed to measure citrate concentrations without additional dilution in systemic plasma (range 0.1–4 mmol/L) and with 1:2 sample dilution in circuit plasma or ultrafiltrate (range 0.2–8 mmol/L). Twelve patients (Tab. 1) with septic shock and liver dysfunction (on CVVHDF at low blood flow and citrate anticoagulation) were studied *ex vivo* for citrate levels in systemic and circuit blood and in ultrafiltrate (at 0, 0.5, 1, 3, 6, 9, 12, 24, 48 and 72 hrs).

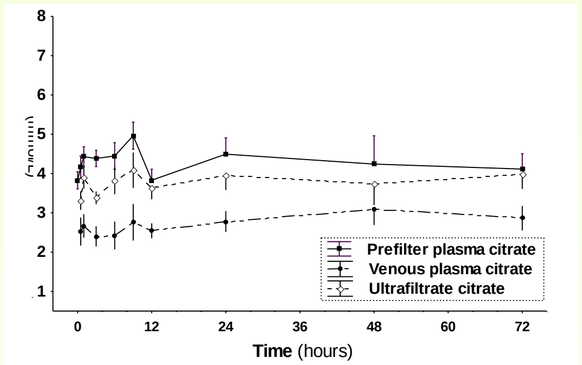

Fig 2: : Citrate levels in prefilter and venous plasma and in effluent during CVVHDF

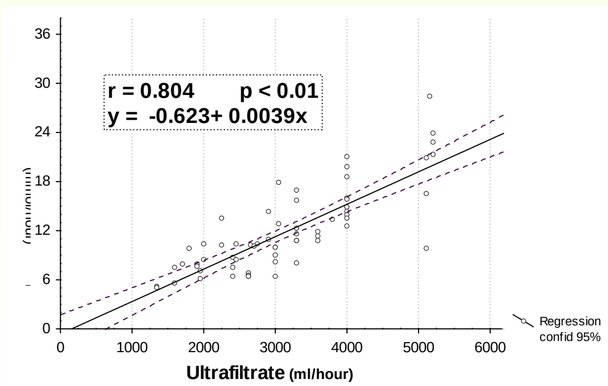

Fig 3: Correlation between loss of citrate and ultrafiltrate volume.

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Results

By studying in vitro the blood distribution of citrate between intra- and extracellular compartments, we found a significant correlation (r= 0.9997, y= 0.00066 + 1.020x, n= 36) between the plasma measured and the predicted citrate concentrations for an exclusive extracellular distribution (taking into account the hematocrit value). In vivo median systemic arterial citratemias were 0.09 (0.06-0.12) mmol/L (time 0) and 0.23 (0.18-0.31) mmol/L during CVVHDF (Figure 1). No significant correlation was found between systemic plasma citrate and total calcium levels, ionized calcium or total/ionized calcium ratio.

Figure 2 shows circuit prefilter, circuit venous and effluent citrate values. The overall median citrate concentrations were 4.02 (3.62-4.89) mmol/L in prefilter plasma, 2.51 (1.76-3.40) mmol/L in venous plasma and 3.69 (3.29-4.21) mmol/L in effluent. Median sieving coefficient for citrate calculated with different volumes of CVVHDF ultrafiltrate from 1350 to 5100 ml/hour was 0.95 (0.88-1.02, n= 43).

Citrate net removal (Figure 3) and total calcium loss (Figure 4) significantly correlated with the effluent volume (r= 0.85 and 0.78, respectively). Median citrate load entering in patient bloodstream was as low as 13.60 (9.1-19.6, n 68) mmol/hour. Although cost analysis of citrate test demonstrated an increased daily cost (from 2.96 to 3.51 Euro), saving costs could be potentially relevant if test availability allowed a more extended use of citrate anticoagulation (longer filter survival and reduced hemorrhagic complications).

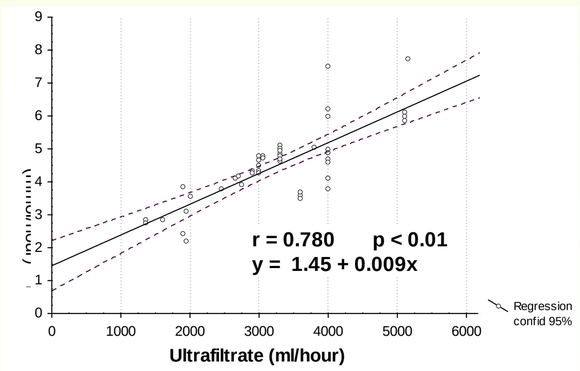

Fig 4: Correlation between loss of total calcium and ultrafiltrate volume.

Conclusions

In septic shock patients with liver dysfunction, the routine determination of citrate may be a useful tool in guiding the clinical application of citrate anticoagulation in RRT. In our study, we observed that by increasing the dialysate volume, we could obtain a lower total citrate patient load and thus were able to maintain blood citrate within a safe range.

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