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Regional citrate anticoagulation for slow continuous ultrafiltration: risk of severe metabolic alkalosis

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Abstract

Background. Slow continuous ultrafiltration (SCUF) is a safe and efficient treatment for fluid overload in patients who are hemodynamically unstable, have low urine output, and are not in need of dialysis or hemofiltration for solute clearance. Sustained anticoagulation is required for these long treatments, thus posing clinically challenges for patients having contraindications to systemic anticoagulation with heparin. Regional citrate anticoagulation would be an alternative option; however, we believed that this would be problematic due to citrate kinetics that predicted the development of metabolic alkalosis.

Methods. In that patients' serum bicarbonate reached 45 mEq/L and arterial pH rose to 7.59 after just 3 days of SCUF, we developed equations to study this phenomenon. We report here the acid–base balance calculations quantifying base accumulation in SCUF compared to continuous venovenous hemofiltration (CVVH).

Results. This kinetic approach demonstrates the importance of accounting for the high citrate clearance into CVVH hemofiltrate, which prevents development of the alkalosis seen with the relatively low ultrafiltration rates in SCUF: there was net bicarbonate accumulation of ~1400 mmol/day with SCUF, compared to 664 to as low as 274 mmol/day during CVVH. The calculations underscore the importance of the relative fluid flow rates as well as the bicarbonate and citrate levels in the various infused solutions. We also discuss how citrate's acid–base effects are potentially complicated by metabolism via gluconeogenic and ketone body pathways.

Conclusions. These acid–base balance findings emphasize why clinicians must be mindful of the risk of metabolic alkalosis when using continuous renal replacement therapy modalities with low rates of ultrafiltration, which thereby presents a contraindication for using citrate anticoagulation for SCUF.

Keywords: anticoagulation; citrate; CVVH; metabolic alkalosis; SCUF

Introduction

Based on its calcium ion-chelating properties, citrate has been successfully used to regionally anticoagulate extracorporeal circuits. Although acid–base disturbances were not problematic when used for intermittent hemodialysis treatments [1], there was a concern that for CRRTs prolonged citrate infusions would generate enough bicarbonate so as to induce metabolic alkalosis. Indeed, in an early report [2] of continuous venovenous hemodialysis (CVVHD), metabolic alkalosis was a clinical problem. This phenomenon has not been an issue in multiple more recent publications, ranging from small to large, single and multi-center series [3–6], and is primarily due to these protocols having greater extracorporeal clearance of citrate. The effect of effluent/dialyzate volume on citrate clearance and attenuation of alkalosis has been highlighted in recent reports [7, 8]. In that lower effluent volumes predict lower citrate removal, we believed that a situation exemplifying the risk of citrate-induced alkalosis would be the very slow filtration rates occurring during continuous ultrafiltration (UF) (SCUF, e.g. 3 versus 50 L effluent/day): a problem that we had encountered in two individuals (serum bicarbonate 45 mEq/L, arterial pH 7.59). The goal of this study was to use a mass balance approach to quantify the acid–base parameters, to explain the alkalosis and thereby to highlight for clinicians the heretofore unreported dangers (i.e. contraindication) of using citrate as an anticoagulant for SCUF.

Methods

We modeled the base buffer balance during 3 days of SCUF with that of CVVH using predilution of replacement fluid. Our regional citrate anticoagulation protocol results in a filter life in excess of 50 h and has been previously reported: anticoagulant citrate dextrose solution A (ACD-A) containing 116 mmol citrate/L is infused pre-filter at 220 mL/h.

For calculations, we used an initial plasma citrate concentration of zero, and steady state values as low as 0.3 mmol/L and as high as 1 mmol/L. Citrate losses into the hemofiltrate effluent are based on the net citrate concentration of the fluid entering the filter, which results from (i) the mixture of citrate and blood during SCUF plus the pre-dilution replacement fluid during CVVH; (ii) the proportionality of those fluid flow rates (blood flow 100 mL/min, CVVH pre-filter replacement fluid at 3 L/h); (iii) the hematocrit (30% for calculations); (iv) baseline normal plasma bicarbonate levels; (v) replacement fluid having a bicarbonate concentration of either 24 or 32 mmol/L; (vi) net UF rate of 200 mL/h and (vii) an assumed 1:1 plasma-to-filtrate losses for the small molecular weight molecules of citrate and bicarbonate [9]. For example, for each 150 mL/min of the pumped mixture of blood and pre-dilution replacement fluid, there is 70 mL/min plasma [100 mL/min blood $\times$ (1 $-$ Hct)] plus the 50 mL/min of substitution fluid (3 L/h). Thus, the hemofiltration effluent would represent 70/120 (58%) plasma and 50/120 (42%) fluid. This proportionality would change accordingly for protocols that involve other pre-filter infusions. For each solute, one would measure the solute concentration in the hemofiltrate, calculate daily losses using effluent volume and then calculate mass balance based on the levels in plasma, replacement fluid or any other infusion prescribed.

The equations below demonstrate the general approach to the calculations, which would need to be customized for each facility's protocol so as to account for all fluids depending on whether they are administered pre-filter versus post-filter, their respective flow rates and their typically disparate units of measure for mass and time intervals. In the equations below, B = blood; A = anticoagulant (i.e. citrate) solution; R = replacement fluid wherein R* = that administered pre-filter; O = other administered fluid, if applicable; Q = the flow rate for the respective fluid; [solute] = concentration of the desired substance (i.e. citrate or bicarbonate) and the rates are per 24 h. Thus in SCUF $Q_R = 0$, while it is >0 for CVVH. If the replacement fluid is given, post-filter then $Q_{R^*} = 0$.

Practitioners performing these calculations need to be cognizant that the equations do not include the complexities of kinetics involving more than a single compartment for citrate nor would this simplified approach using single blood values predict steady state levels. The literature includes analogous calculations, such as for the dialysance and kinetics of both citrate and calcium [10]. Algorithms would also need to be adjusted for those facilities that utilize devices that generate large-volume batches of customizable replacement fluid, especially those which can incorporate citrate into those solutions (rather than separate infusions) [11]. The clinical value of this approach was highlighted by the experience with two patients undergoing 3 days of 5 L/day SCUF under conditions similar to those modeled here. In both cases, the bicarbonate concentration rose from ~25 mEq/L to the range of 41–45 mEq/L with arterial pH as high as 7.59.

$$\text{Solute loss} = \left(\frac{[\text{solute}_B] \cdot [Q_B \cdot (1 - \text{Hct})] + [\text{solute}_A] \cdot Q_A + [\text{solute}_R] \cdot Q_{R^*} + [\text{solute}_O] \cdot Q_O}{[Q_B \cdot (1 - \text{Hct})] + Q_A + Q_R + Q_O} \right) \cdot Q_{\text{Hemofiltrate}}$$

$$\text{Solute added} = [\text{solute}_A] \cdot Q_A + [\text{solute}_R] \cdot Q_R + [\text{solute}_O] \cdot Q_O$$

Results

During SCUF, base buffer gained by the patient was solely the consequence of citrate infusion, as no bicarbonate was administered. Conversely, buffer losses into the ultrafiltrate were a mixture of those originating from the plasma (initially only bicarbonate because the citrate level was zero at the start of the treatment) and from the ACD-A which had been infused into the blood pre-filter. Based on the proportionality of those fluid infusion rates and the blood having 70% plasma, the effluent for SCUF was 95% plasma and 5% ACD-A. The effluent for CVVH was composed of 56.5% plasma, 3.2% ACD-A and 40.3% replacement fluid. For the Days 0–1, 1–2 and 2–3 time intervals, the in/out buffer and net balance values were calculated for SCUF and are shown in Table 1.

For the first 3 days, there was a net loss of plasma bicarbonate of 264, 313 and 372 mmol/day, respectively. Assuming a low plasma level of citrate (0.3 mmol/L), there was only a small amount of those losses into the ultrafiltrate. The net result for each of those days was a gain of citrate of 549 mmol/day. Table 2 demonstrates the net acid–base balance when the metabolism of one citrate molecule leads to the generation of three bicarbonates: a very positive bicarbonate balance of 1383, 1334 and 1275 mmol/day for the first 3 days, respectively, and thereby explaining the development of the metabolic alkalosis. This can be put in the perspective of published reports [2, 12, 13] of patients having a somewhat greater citrate accumulation in the plasma, i.e. up to 1 mmol/L rather than 0.3 mmol/L. In those circumstances, the calculations show that there are only small increases in citrate losses into the ultrafiltrate, and the net bicarbonate balance remains very similar for the corresponding 3 days: +1362, 1313 and 1254 mmol/day for plasma citrate of 1 mmol/L.

Our balance calculations showed very different findings for CVVH. Table 1 compares the acid–base results of replacement fluids that had a bicarbonate concentration of 24 versus 32 mmol/L over 1 day (since we have not encountered progressive alkalosis). With the commonly used 24 mmol/L of bicarbonate in the prediluted replacement fluid, the net bicarbonate losses were ~230 mmol/day. For citrate balance, when its plasma level was relatively low (0.3 mmol/L), there was a net gain of 264 mmol/day. Thus, with a 1:3 production of bicarbonate from citrate, the net bicarbonate balance was +664 mmol/day, which was ~48% of that observed with SCUF. When plasma citrate rises to 1 mmol/L, that molecule has greater losses into the filtrate. This results in a net +553 mmol/day of bicarbonate during CVVH, which is 41% of the SCUF value. When replacement fluids with the higher bicarbonate concentration of 32 mmol/L are utilized, there is a corresponding greater net bicarbonate balance, somewhat attenuating the differences between SCUF and CVVH: +975 or 864 mmol/day for the corresponding plasma citrate levels of 0.3 or 1 mmol/L. These CVVH values are ~70 or 63% of the bicarbonate accumulation anticipated with SCUF.

Table 1. Bicarbonate and citrate balance during SCUF and CVVH with regional citrate anticoagulation[a]

		SCUF			CVVH	
					Replacement fluid bicarbonate	
	Source	Day 0–1 (mmol/L)	Day 1–2 (mmol/L)	Day 2–3 (mmol/L)	24 mmol/L	32 mmol/L
Buffer in						
Bicarbonate	Replacement fluid	n/a	n/a	n/a	1728	2304
Citrate	ACD-A	612	612	612	612	612
Buffer out						
Bicarbonate	Plasma	−264	−313	−372	−1162	−1162
	Replacement fluid	n/a	n/a	n/a	−796	−1061
	Total	−264	−313	−372	−1958	−2223
Citrate	Plasma[b]	−3	−3	−3	−14	−14
	ACD-A	−60	−60	−60	−305	−305
	Total	−63	−63	−63	−314	−314
Net bicarbonate		−264	−313	−372	−230	81
Net citrate		549	549	549	298	298

[a]n/a, not applicable.
[b]Assumes plasma citrate 0.3 mmol/L.

Table 2. Net bicarbonate balance during SCUF and CVVH with regional citrate anticoagulation

		SCUF			CVVH	
					Replacement fluid bicarbonate	
	Source	Day 0–1	Day 1–2	Day 2–3	24 mmol/L	32 mmol/L
Procedure's bicarbonate balance (mmol/day)	Plasma and fluids	−264	−313	−372	−230	81
Procedure's citrate balance (mmol/day)	Plasma and fluids[a]	549	549	549	298	298
Bicarbonate generation (mmol/day)	Citrate metabolism	1647	1647	1647	894	894
Net bicarbonate balance (mmol/day)		1383	1334	1275	664[b]	975[c]

[a]Assumes plasma citrate 0.3 mmol/L.
[b]48% of the initial SCUF value compared to 41% (553 versus 1362 mmol/day) when the plasma citrate is 1 mmol/L.
[c]70% of the initial SCUF value compared to 63% (864 versus 1362 mmol/day) when the plasma citrate is 1 mmol/L.

Discussion

While widely acknowledged to be an excellent extracorporeal regional anticoagulant, the routine use of citrate for CRRT has been limited, due in part to concerns over its metabolism and potential toxicity [13]. At one end of the clinical spectrum is impaired degradation (i.e. 'citrate lock' with severe hepatic failure [12]), while the opposite circumstance is complete conversion, yielding high levels of its end products. Because metabolism of each mole of citrate generates 3 moles of bicarbonate, there is the risk of developing severe metabolic alkalosis from large cumulative doses of the anticoagulant. In an early CVVHD protocol that utilized dialyzate rates as low as 1 L/h, Mehta *et al.* [2] reported alkalemia in 3 of 18 subjects, with the pH rising as high as 7.54. Those patients were treated with HCl infusions to correct the alkalosis. As described and quantified in multiple subsequent publications, however, we believe that highly positive citrate balance is prevented in protocols that prescribe much higher hemofiltrate/UF rates and thereby provide greater buffer clearance. In the series of Morgera *et al.* [14], for example, approximately half of the patients who received citrate (as the sole or as part of combination anticoagulation protocols) developed alkalosis, which was resolved by higher dialyzate rates. Similarly, Mariano *et al.* [7] described how increasing the dialyzate flow could increase citrate losses up to ~60% of the amount infused. The literature demonstrates that it is possible to devise protocols which adjust the infusion rates of citrate and/or bicarbonate-containing solutions so as to avoid acid–base disturbances at the same time as achieving long filter lives [6, 11, 15–18]. We hypothesized that SCUF would exemplify circumstances which would be characterized by low citrate removal and thus a high risk for alkalosis. Our net balance calculations quantified of this base accumulation: using a plasma citrate value of 0.3 mmol/L and replacement fluid bicarbonate at 24 mmol/L, we demonstrated that net bicarbonate balance was a positive 1383 mmol/day with 5 L/day SCUF compared to 664 mmol/day (48% of the SCUF value) with CVVH, thereby explaining the development of the severe metabolic alkalosis. The calculations also provide insight into how mass clearance changes when there are small increases in plasma citrate concentration and thereby enhanced removal into the hemofiltrate or ultrafiltrate. This analysis is difficult because of the range of plasma citrate values in the literature, which corresponds to widely different citrate infusion protocols. Reported levels include those up to 0.31 [9], 1.01 (1.60 with cirrhosis) [12] and as high as 2.95 mmol/L [2]. Should plasma citrate rise from 0.3 to 1 mmol/L, the bicarbonate balance during CVVH would be 41% of that with SCUF. Lastly, the balance equations

quantify the additional net bicarbonate provided when its concentration in the CVVH replacement fluid is raised from 24 to 32 mmol/L: an extra ~150–300 mmol/day (depending on the plasma citrate level), which may be appropriate in circumstances of severe metabolic acidosis and very high catabolic rate.

The impact of a net positive citrate balance can be appreciated on the basis of the metabolic fate for this buffer/chelator. While clinical concern has centered on bicarbonate generation from citrate degradation, the citrate pathway is neither straightforward nor the only possible fate of the buffer. Surprisingly, little is known about how humans handle high loads of citrate, such as those described in this report. As shown in Figure 1, each 'turn' of the tricarboxylic acid (TCA or Krebs cycle) cycle forms 2 moles of bicarbonate and 1 mole of oxaloacetate. Citrate is also converted to oxaloacetate and acetyl-CoA by ATP-citrate lyase. Fatty acid biosynthesis is another metabolic fate of acetyl-CoA produced in the lyase reaction. Oxaloacetate may undergo NADH-dependent reduction to malate by malate dehydrogenase, followed by the formation of NADPH (a fuel for fatty acid formation) by the malic enzyme, the latter producing bicarbonate. Oxaloacetate is also a substrate for gluconeogenesis, which, along with glycolysis, determines pyruvate availability for fueling the TCA cycle. Although not indicated in Figure 1, intracellular transport of citrate between cytosolic and mitochondrial compartments is mediated by the citrate transport protein [19], an electroneutral co-transporter of oxaloacetate (and other dicarboxylic acids) and protonated citrate (reaction: $HCitrate^{2-}_{cyto} + Oxaloacetate^{2-}_{mito} \rightarrow HCitrate^{2-}_{mito} + Oxaloacetate^{2-}_{cyto}$). Evaluation of the relative contributions of these pathways to citrate utilization during SCUF lies beyond the scope of this report. It is sufficient to say that citrate can lead to bicarbonate formation, directly via the TCA cycle or indirectly through the formation of oxaloacetate. The latter leads back to the TCA cycle or indirectly through gluconeogenesis and glycolysis to generate pyruvate, which is a substrate for pyruvate dehydrogenase (decarboxylating) and pyruvate carboxylase. The portion of the large citrate load that instead serves as a substrate for gluconeogenesis or fatty acid production (Figure 1) remains to be determined in these patients.

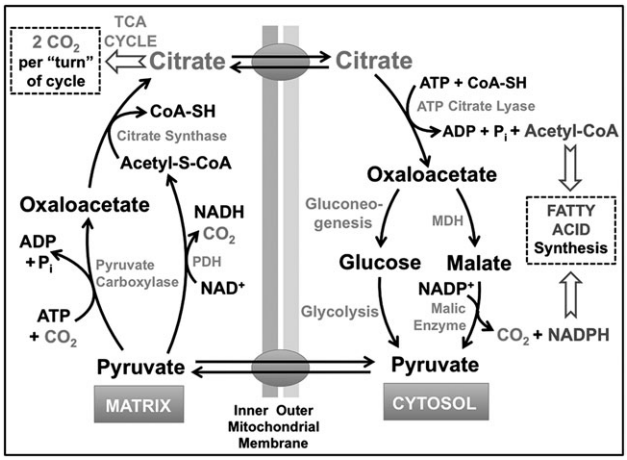

Fig. 1. Diagram for citrate metabolism and bicarbonate formation. Shown are key enzymatic reactions catalyzing the formation and degradation of citrate and oxaloacetate, the latter an important metabolite in the TCA (Krebs) cycle, gluconeogenesis as well as the formation of reducing equivalents required for fatty acid biosynthesis. Note that each turn of the TCA cycle generates 2 moles of bicarbonate. The relative flux of oxaloacetate through gluconeogenesis versus the steps catalyzed by MDH and malic enzymes will depend on other metabolic circumstances beyond the scope of this discussion. MDH, malate dehydrogenase; PDH, pyruvate dehydrogenase; acetyl-*S*-CoA, acetyl-*S*-coenzyme A.

In conclusion, depending on the choice of fluids and flow rates, CVVH has bicarbonate accumulation as low as 20–48% of the balance occurring with SCUF. Thus, due to the risk of developing severe metabolic alkalosis, there is a relative contraindication in using regional citrate anticoagulation for SCUF.

Conflict of interest statement. None declared.

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