Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients

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Objectives: **To investigate pharmacokinetics and metabolism of sodium citrate in critically ill patients. To determine the risk of citrate accumulation in the setting of liver dysfunction (cirrhosis, hepatorenal syndrome).**

Design: **Prospective cohort study.**

Setting: **Intensive Care Unit, Department of Medicine IV, University Hospital Vienna.**

Patients: **Consecutive critically ill cirrhotic (n = 16) and noncirrhotic patients (n = 16).**

Interventions: **Infusion of sodium citrate (0.5 mmol·kg^{-1}·hr^{-1}) and calcium chloride (0.17 mmol·kg^{-1}·hr^{-1}) for 2 hrs. Analysis of serial arterial blood samples.**

Measurements and Main Results: **Total body clearance of citrate was normal in noncirrhotic critically ill patients but significantly reduced in cirrhotic patients (710 vs. 340 mL/min, $p = .008$). Citrate peak concentrations and concentration over time were increased by 65% and 114% in cirrhotic patients ($p < .001$), respectively; volumes of distribution were similar. Net metabolic changes were quantitatively similar, with pH and plasma bicarbonate concentrations increasing more slowly in cirrhotic patients. No citrate-related side effects were noted. Citrate clearance could not be predicted by standard liver function tests and was not appreciably influenced by renal function and Acute Physiology and Chronic Health Evaluation II scores.**

Conclusions: **This first systematic study on citrate pharmacokinetics and metabolism in critically ill patients confirms a major role of hepatic citrate metabolism by demonstrating reduced citrate clearance in cirrhotic patients. Pharmacokinetic data could provide a basis for the clinical use of citrate anticoagulation in critically ill patients. Provided dose adaptation and monitoring of ionized calcium, citrate anticoagulation seems feasible even in patients with decompensated cirrhosis. Metabolic consequences of citrate infusion were not different between groups in this study but may be more pronounced in prolonged infusion. (Crit Care Med 2003; 31:2450–2455)**

KEY WORDS: citrate; alkalosis; ionized calcium; cirrhosis; regional anticoagulation

Regional anticoagulation with sodium citrate acts by chelating calcium in the extracorporeal circulation and is increasingly recognized as an alternative to heparin in critically ill patients with a high risk of bleeding (1–3). Citrate reduces hemorrhage and improves patency, clearance rates, and biocompatibility of hemofilters, (4) mainly due to a reduced activation of systemic and dialyzer coagulation (5, 6). Inhibition of calcium-mediated activation of inflammatory cells in the extracorporeal circuit might confer additional benefits (7). For instance, citrate could prevent disseminated intravascular coagulation, which is a frequent complication in patients with liver failure on extracorporeal detoxification (8). In chronic hemodialysis, the use of citrate prevents heparin-induced thrombocytopenia, hyperlipidemia, osteoporosis, and alopecia (9).

Under physiologic circumstances, citrate undergoes rapid metabolism, which occurs mainly in the liver and to a lesser extent in other tissues such as skeletal muscle and renal cortex (10). In critically ill patients, pharmacokinetics of exogenous citrate are unknown so far. However, impaired citrate metabolism has been described in patients with acute liver failure (11, 12) and during the anhepatic phase of liver transplantation (13, 14). It is unknown whether critically ill cirrhotic patients are at risk of citrate accumulation.

This study tested the hypothesis that citrate metabolism would be impaired in critically ill cirrhotic patients. As a further goal, we investigated citrate pharmacokinetics and metabolic implications to provide a basis for the clinical application of citrate anticoagulation in critically ill patients. Finally, we investigated whether citrate clearance could be predicted from routine variables of hepatic function.

MATERIALS AND METHODS

Patients. Inclusion criteria for the study were admission to the intensive care unit, age 19–75 yrs, and presence of cirrhosis (cirrhotic group) documented either by histology or by the typical clinical criteria of coagulopathy, splenomegaly, ascites, and esophageal or gastric varices. As a control group, consecutive critically ill patients without cirrhosis or relevant hepatic dysfunction were evaluated. Exclusion criteria for both groups were marked alkalosis (pH >7.55), blood or plasma transfusion within 48 hrs before study, ionized hypocalcemia (Ca^{2+} <0.95 mmol/L), lactic acidosis, hemodynamic instability requiring vasopressor support, and use of citrate-containing medications. All patients received central venous and arterial catheters. Electrocardiogram was continuously monitored to record heart rate and detect hypocalcemia-induced arrhythmia. The study protocol was

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approved by the Ethics Committee of the Vienna Medical School, and informed consent was obtained from patients or their next of kin.

Citrate and Calcium Infusions. Trisodium citrate (0.5 mol/L [147.05 g/L]; Maierhofer Pharma, Linz, Austria) was infused via a central catheter at 0.5 $mmol \cdot kg^{-1} \cdot hr^{-1}$ for 2 hrs to achieve steady-state conditions. $CaCl_2$ (0.5 mol/L, Maierhofer Pharma, Linz, Austria) was administered via a separate lumen at 0.17 $mmol \cdot kg^{-1} \cdot hr^{-1}$. This dose, which exceeds current recommendations, (15) was chosen to safely prevent hypocalcemia given reduced plasmatic calcium stores in critically ill and cirrhotic patients. No patient required calcium supplementation after the end of infusion.

Arterial blood samples were obtained at baseline and after 10, 20, 40, 60, 120 (end of infusion), 125, 130, 140, 160, 180, 210, and 240 mins. Blood gas samples were collected in a lithium heparin syringe and immediately processed by a ABL 700 (Radiometer Copenhagen, Brønshøj, Denmark) for blood gas, electrolytes, and ionized calcium analysis (Ca^{2+} ion selective electrode). Baseline routine blood chemical values were measured by a Hitachi Autoanalyzer (Roche Diagnostics, Mannheim, Germany), and full blood counts were measured by a Sysmex Hematology Analyzer (TAO Medical Electronics Company, Kobe, Japan). Serum aliquots were stored at −30°C until further analysis. Citrate concentrations were measured using a commercially available test kit (citrate lyase ultraviolet method, R-Biopharm, Darmstadt, Germany) (16). Total calcium concentrations at 0, 20, 60, 120, 130, 160, and 240 mins were measured photometrically using an Integra 700 (Roche Diagnostics, Mannheim) in a proportion of samples (n = 60).

Pharmacokinetic Calculations. Pharmacokinetic analysis was performed with a computer program (Kinetica 2.0; Innaphase Sarl, Paris, France) using noncompartmental approaches. Baseline plasma concentrations of citrate were set to zero. Area under the concentration time-curve was calculated from nonfitted data by employing the linear trapezoidal rule. The start time for calculation of the smallest (slowest) disposition rate constant (Lz) was set to 120 mins. The following main pharmacokinetic variables were determined: area under the concentration time curve from 0 to 4 hrs (AUC), maximum concentration (C_{max}), time to maximum concentration (t_{max}), and the half-life calculated for the terminal slope ($T_{1/2}$). Citrate clearance and the apparent volume of distribution (Vd_z) and volume of distribution at steady state (Vd_{ss}) were calculated by use of standard procedures. The apparent volume of distribution (Vd_z) was calculated by the equation Vd_z = dose × Lz /AUC. Vd_{ss} was calculated by the equation Vd_{ss} = dose × MRT/AUC, where MRT represents the mean residence time of a molecule.

Data Analysis. Data are presented as mean (SD) unless indicated otherwise. We considered $p < .05$ (two-tailed test) to be statistically significant. Normal distribution of samples was tested with the Kolmogorov-Smirnov test. Comparison between groups was performed using Student's *t*-test or Mann Whitney *U* test (according to data distribution) and Fisher's exact test for categorical variables. The ratio of total to ionized calcium (Ca_{tot}/Ca^{2+}) was calculated for a proportion of samples in both groups (n = 60). The influence of potential confounding variables (Acute Physiology and Chronic Health Evaluation II, creatinine clearance) on pharmacokinetic results (AUC, citrate clearance) was investigated with a linear regression model. We also investigated whether citrate clearance could be predicted by routine tests of liver function using a stepwise linear regression model.

RESULTS

Baseline Characteristics. Clinical characteristics of both groups of patients are represented in Table 1. Causes of intensive care unit admission in cirrhotic patients were pneumonia (n = 3), hemodynamic monitoring after gastrointestinal bleeding (n = 3), hepatorenal syndrome (n = 5), and pulmonary edema, hepatic encephalopathy, urosepsis, acute renal failure, or osteomyelitis (n = 1 each). Twelve cirrhotic patients were mechanically ventilated. Nine patients had moderate ascites; two patients had tense ascites. Noncirrhotic control patients were admitted due to cardiopulmonary resuscitation (n = 4), pneumonia, cardiac decompensation, acute renal failure (n = 3 each), open heart surgery, sepsis, and pulmonary embolism (n = 1 each). All control patients were mechanically ventilated. Blood pressure was not different between groups; heart rate was increased in cirrhotic patients (Table 1).

Details of blood chemistry and hematologic variables are represented in Table 2. As expected, baseline concentrations of bilirubin and lactate were increased and coagulation tests were impaired in cirrhotic patients. Plasma concentrations of aspartate aminotransferase were increased in the noncirrhotic group, but there was no difference in alanine aminotransferase concentrations, blood gas analysis, acid-base state, electrolyte concentrations, and variables of renal function. In the control group, all but one baseline concentration of citrate were within the normal range (<0.17 mmol/L) (17). In contrast, all cirrhotic patients showed increased citrate concentrations at baseline (Table 3).

Citrate Pharmacokinetics. Main pharmacokinetic results are provided in Table 3. Citrate serum concentrations during and after the infusion of sodium citrate are represented in Figure 1*A*. Compared with control patients, citrate concentrations were increased at baseline, at 120 mins (60%), and at end of the study (287%), contributing to a significant difference in AUC (115%, Table 3). Accordingly, steady-state clearance of citrate was reduced (48% of controls) and $T_{1/2}$ was prolonged in cirrhotic patients (69 vs. 36 min, Table 3). No difference in T_{max}, V_{dz}, and V_{ss} was observed. Citrate clearance could not be predicted with sufficient accuracy from standard liver function tests. Stepwise linear regression did not identify an appreciable influence of creatinine clearance and Acute Physiology and Chronic Health Evaluation II scores on citrate clearance.

Calcium Concentrations. Total and ionized calcium concentrations at baseline were similar (Table 2). Also the increase in total calcium concentrations at 2 and 4 hrs was not different between cirrhotic (1.0 and 0.6 mmol/L, respectively) and noncirrhotic patients (0.9 and 0.6 mmol/L, respectively, p = nonsignificant). Ca^{2+} tended to be lower in cir-

Table 1. Clinical characteristics of study population

	Cirrhotic Patients	Control Group	*p* Value
Age, yrs	55 ± 10	59 ± 17	.45
Sex, male/female	6/10	7/9	1.00
Weight, kg	77 ± 21	72 ± 10	.40
Heart rate	102 ± 21	82 ± 19	.01
Mean blood pressure	79 ± 17	85 ± 17	.35
Urine output, mL/day	1655 ± 1050	2290 ± 603	.27
Creatinine clearance, mL/min	71 ± 74	67 ± 61	.89
APACHE II score	18 ± 8	18 ± 9	.95

APACHE, Acute Physiology and Chronic Health Evaluation.
Data are represented as mean ± SD.

Table 2. Baseline laboratory characteristics

	Normal Range	Cirrhotic Patients	Control Group	*p* Value
Glucose, mg/dL	76–110	172 ± 37	148 ± 32	.05
Bilirubin, mg/dL	0.2–1	13.2 ± 13.3	1.9 ± 2.8	.004
Albumin, g/L	34–48	23 ± 4	24 ± 5	.60
Alanine aminotransferase, U/L	0–18	20 ± 18	57 ± 55	.02
Aspartate aminotransferase, U/L	0–23	38 ± 24	46 ± 47	.55
Lactate dehydrogenase, U/L	120–140	259 ± 137	442 ± 358	.07
Hemoglobin, g/dL	12–18	9.3 ± 1.1	10.1 ± 1.4	.10
Platelets, G/L	150–350	71 ± 40	139 ± 100	.02
White blood cells, G/L	4–10	10.1 ± 4.4	12 ± 7	.72
Prothrombin time index, %	75–140	25 ± 14	64 ± 18	<.001
APTT, sec	27–41	59 ± 16	42 ± 9	.001
Fibrinogen, mg/dL	180–390	192 ± 102	470 ± 173	<.001
pH	7.35–7.45	7.422 ± 0.061	7.437 ± 0.087	.58
$Paco_2$, mm Hg	35–45	36 ± 8	41 ± 11	.12
Pao_2, mm Hg	82–100	72 ± 15	85 ± 23	.07
Base excess	±4	−0.8 ± 4.9	2.8 ± 6.9	.10
Standard bicarbonate, mmol/L	18–23	24 ± 4	27 ± 6	.09
Sodium, mmol/L	135–145	141 ± 9	142 ± 6	.96
Potassium, mmol/L	3.5–5.5	3.6 ± 0.5	4.0 ± 0.6	.34
Total calcium, mmol/L	2.10–2.65	2.0 ± 0.2	1.9 ± 0.2	.09
Ca^{2+}, mmol/L	1.14–1.28	1.12 ± 0.14	1.09 ± 0.11	.53
Lactate, mmol/L	1.0–2.4	2.9 ± 1.2	1.7 ± 1.0	.005
Creatinine, mg/dL	0.5–1.3	1.8 ± 1.2	1.3 ± 0.8	.18

APTT, activated partial thromboplastin time.
Data are represented as mean ± SD.

Table 3. Citrate pharmacokinetics

	Cirrhotic Patients	Control Group	*p* Value
Total dose, mmol	77 ± 21	72 ± 10	.40
$C_{baseline}$, mmol/L	0.51 ± 0.13	0.06 ± 0.13	<.001
C_{max}, mmol/L	1.60 ± 0.50	1.01 ± 0.39	.007
T_{max}, mins	115 ± 12	114 ± 16	.93
AUC, mmol × min/L	282 ± 130	131 ± 68	<.001
$t_{1/2}$, mins	69 ± 33	36 ± 18	.001
Vd_z	27 ± 9	29 ± 10	.52
Vd_{ss}	23 ± 6	21 ± 6	.34
Clearance, mL/min	340 ± 185	710 ± 397	.002

$C_{baseline}$, baseline concentration; C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC, area under the concentration time curve; $t_{1/2}$, citrate half life, Vd_z, apparent volume of distribution; Vd_{ss}, volume of distribution at steady state.
Data are represented as mean ± SD.

rhotic patients throughout infusion (Fig. 1*B*), but this was not associated with clinical symptoms. Ca_{tot}/Ca^{2+} ratio reflecting the relation of protein-bound and citrate-chelated to free calcium was significantly correlated with citrate concentrations in both cirrhotic ($R = .50$, $p < .001$) and noncirrhotic patients ($R = .62$, $p < .001$). Nonetheless, a Ca_{tot}/Ca^{2+} ratio >2.5 identified only three of 15 samples with citrate concentrations >1.5 mmol/L in cirrhotic and none of two such samples in control patients.

Metabolic Effects. Acid-base status at baseline was comparable between groups (Table 2). Plasma bicarbonate and pH increased more readily in noncirrhotic patients (Fig. 1, *C* and *D*), whereas net pH changes over the whole study period were not different between groups (0.032 in cirrhotic and 0.036 in noncirrhotic patients, p = nonsignificant, Fig. 1*D*). The incidence of moderate (pH >7.45) or severe alkalosis (pH >7.50) during and after infusion was not different between cirrhotic patients (nine and three patients, respectively) and controls (13 and six patients, respectively, p = nonsignificant).

DISCUSSION

This study provides the first data on citrate pharmacokinetics and metabolism in critically ill patients. Our data demonstrate that citrate clearance is impaired in cirrhotic relative to noncirrhotic critically ill patients and confirm the major role of hepatic citrate metabolism. Net metabolic effects of citrate were quantitatively similar in the two groups, although bicarbonate and pH increased more readily in noncirrhotic patients. These effects reflect impaired citrate metabolism in cirrhosis and may be more pronounced in long-term or continuous citrate infusion. No citrate-related side effects were observed, confirming that citrate toxicity occurs exclusively in the setting of ionized hypocalcemia (13). Consequently, provided close monitoring of Ca^{2+} and substitution of calcium, regional citrate anticoagulation seems feasible even in patients with advanced cirrhosis, although optimal citrate dose in this setting remains to be defined by additional studies (18).

Citrate anticoagulation is theoretically very attractive for patients with hepatic failure since it effectively reduces the substantial risk of bleeding associated with heparin anticoagulation for extracorporeal therapies in these patients. In cirrhotic patients, the use of heparin additionally is hampered by low concentrations of antithrombin III, which frequently leads to a coincidence of extracorporeal clotting and clinical bleeding (19). The potential clinical risk and metabolic implications of regional citrate anticoagulation in cirrhosis are unknown, which has prevented its clinical use (20). Because clinical symptoms of hypocalcemia are not reliable in critically ill patients, (21) citrate pharmacokinetics are required (22, 23). It is important to recognize that noncirrhotic critically ill patients metabolized citrate at rates comparable to stable outpatients undergoing therapeutic apheresis (11). In contrast, citrate baseline and peak concentrations, AUC, and elimination half-life were increased in cirrhotic patients, with clearance rates of only 48% relative to controls (Table 3). Single-dose and steady-state volumes of distribution were not different between groups. Citrate clearance rates in cirrhotic patients were still considerably higher than reported for a small group of patients with fulminant hepatic failure (11). Notably, clinical toxicity has been reported exclusively in patients with fulminant hepatic failure or during the anhepatic phase of liver transplantation (12–14).

In both groups of patients, citrate pharmacokinetics could not be predicted by standard laboratory variables of he-

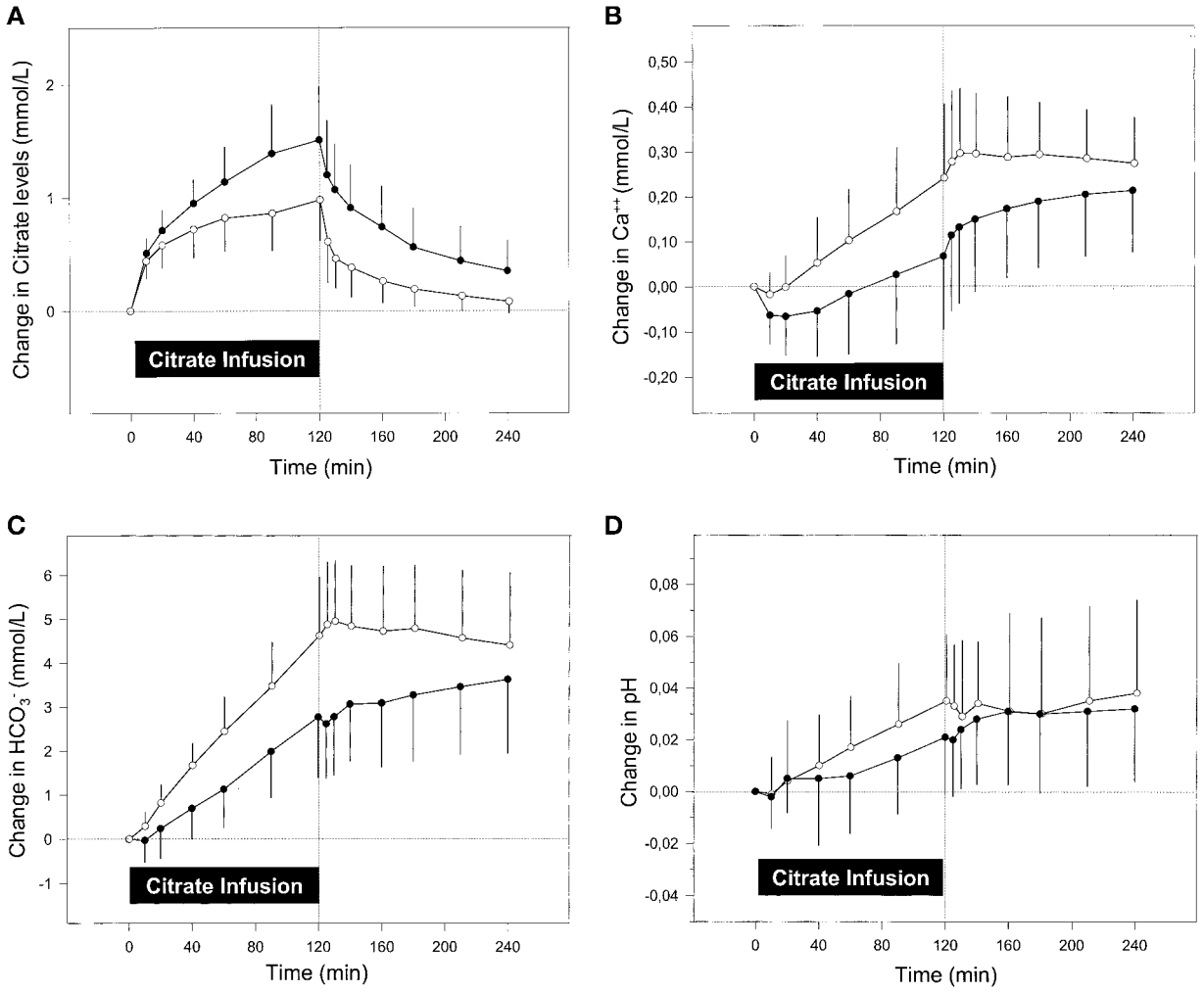

Figure 1. Comparison of cirrhotic (*filled circles*) and noncirrhotic (*open circles*) critically ill patients with respect to concentrations of citrate (*A*), ionized calcium (*B*), standard bicarbonate (*C*), and blood pH (*D*) during and after a 2-hr infusion of sodium citrate (0.5 mmol·kg^{-1}·hr^{-1}) and calcium chloride (0.17 mmol·kg^{-1}·hr^{-1}). Data are represented as mean ± SD

patic function (which certainly cannot fully represent the complex metabolic functions of the liver). All cirrhotic patients but only a single control patient showed increased baseline concentrations of citrate, which is a new and interesting observation. Since patients receiving blood products and citrate-containing medication were excluded, effects of exogenous citrate load are unlikely. Analytical interference with bilirubin also can be excluded ($r^2 = .08$, $p > .60$). Thus, impaired hepatic metabolism of endogenous citrate or—less likely—increased endogenous citrate production in cirrhotic patients could explain the difference.

Meier-Kriesche and colleagues (24) recently reported that a Ca_{tot}/Ca^{2+} ratio >2.5 predicted an increased risk of subsequent hypocalcemia due to citrate accumulation in critically ill patients on citrate hemofiltration. In the current study, a Ca_{tot}/Ca^{2+} ratio >2.5 identified only three of 15 samples with citrate concentrations >1.5 mg/dL in cirrhotic and none of two such samples in control patients. Thus, increased Ca_{tot}/Ca^{2+} ratios could not reliably identify citrate accumulation in this short-term experiment. This can be partially explained by the unusually high calcium supplementation in this study and moderate peak concentrations of citrate (Table 3). Nonetheless, a significant correlation between Ca_{tot}/Ca^{2+} and serum citrate concentrations advocates the use of Ca_{tot}/Ca^{2+} unless citrate measurement becomes routinely available.

Although conversion of citrate to bicarbonate was delayed in cirrhotic patients, net effects on systemic pH did not differ significantly between groups. Both groups of patients developed only mild metabolic alkalosis secondary to citrate metabolism (Fig. 1*D*). It seems noteworthy that bicarbonate generation from citrate could be insufficient for metabolic control in severely acidotic cirrhotic patients. In contrast to high-flux hemodialysis, citrate clearance by hemofiltration (as the method of choice in critically ill patients) rarely exceeds 20%. Citrate-based hemofiltration therefore may account for a citrate load of up to 40 mmol/hr (25). Nonetheless, there are several reports that such treatment was performed without complications in patients with hepatic failure (4). The mean citrate load in our study compares to that of high-flux citrate hemodialysis assuming 50% dialytic clearance or transfusion of approximately 18 units of packed red blood cells anticoagulated with CPDA-1 (6). It is important to point out that, due to reduced plasmatic calcium pools in

Provided citrate infusion rates are adapted and ionized calcium is monitored, citrate anticoagulation seems feasible in patients with advanced cirrhosis, where the advantages compared with heparin are obvious.

hypoalbuminemic patients, close monitoring and sufficient initial substitution of Ca^{2+} are mandatory to prevent hypocalcemia. With increasing release of Ca^{2+} from metabolized citrate, Ca^{2+} infusion rates may be reduced. Considering these precautions, citrate anticoagulation seems feasible even in advanced cirrhosis.

Considering these precautions, citrate anticoagulation seem feasible even in advanced cirrhosis. We are currently evaluating the clinical application of citrate-based high-flux hemodialysis and have not observed any complications in 11 patients with hepatorenal failure treated so far. In continuous treatment, citrate dose should be possibly reduced to prevent accumulation and metabolic derangement in cirrhotic patients. Clearly, more clinical data are required to clarify this issue.

The short duration of citrate infusion is a limitation of the current study, which was primarily designed for pharmacokinetic investigation. It is conceivable that metabolic alkalosis will be more pronounced in long-term use. Patients with hemodynamic instability (excluded in this study for safety reasons) theoretically could demonstrate a more pronounced impairment of citrate metabolism due to failure of microcirculation and oxidative metabolism in conditions such as lactic acidosis and septic shock. Similarly, impaired muscular utilization of citrate could contribute to abnormal citrate metabolism in advanced cirrhosis with cachexia or patients on high doses of vasopressors. Finally, exogenous citrate from blood products could aggravate citrate accumulation and necessitate additional calcium supplementation and/or reduction of citrate infusion rates in cirrhotic patients. There was no appreciable impact of renal function on citrate clearance. According to published literature, a stepwise decrease in the filtered load of citrate occurs with decreasing GFR, whereas renal clearance of citrate is significantly reduced only at higher degrees of renal failure (26). Urinary citrate clearance has been reported to be only 19 ± 9 mL/min in healthy persons (17).

In summary, this study demonstrates that citrate clearance is significantly impaired in cirrhotic relative to noncirrhotic critically ill patients. Short-term metabolic effects were largely comparable to those occurring in noncirrhotic patients, and no adverse events were observed. Citrate metabolism was not confounded by renal function or severity of multiorgan failure and seems to be determined predominantly by hepatic function. Standard liver function tests were unable to predict citrate clearance. Provided citrate infusion rates are adapted and ionized calcium is monitored, citrate anticoagulation seems feasible in patients with advanced cirrhosis, where the advantages compared with heparin are obvious. More data on the clinical application of citrate anticoagulation in liver failure are awaited.

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