Citrate Kinetics in Patients Receiving Long-Term Hemodialysis Therapy

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• ***Background:*** **Regional anticoagulation using sodium citrate is used increasingly in hemodialysis patients at high risk for bleeding. However, citrate metabolism has never been evaluated systematically in hemodialysis patients, and it remains to be shown that citrate is cleared adequately in the presence of renal dysfunction. This study compares the pharmacokinetics of citrate in hemodialysis patients with minimal residual function with that in patients with normal renal function.** ***Methods:*** **Long-term hemodialysis patients (n = 7) and patients without renal failure (n = 11) were investigated during routine immunoadsorption treatment by using a standardized citrate infusion protocol. Serial analysis of blood samples was performed before, during, and up to 120 minutes after citrate infusion (0.33 mmol/kg/h). Citrate plasma concentrations were measured colorimetrically. In addition, ionized calcium, pH, and bicarbonate were measured by using a blood gas analyzer.** ***Results:*** **Basal (0.09 ± 0.03 versus 0.12 ± 0.03 mmol/L; *P* = not significant) and peak citrate concentrations were similar in both groups (1.24 ± 0.42 versus 1.19 ± 0.33 mmol/L; *P* = not significant). Citrate clearance was similar in patients with renal failure (0.31 ± 0.06 L/min) and controls (0.35 ± 0.11 L/min; *P* = 0.47). Effects on pH were minimal and did not differ between groups. No patient developed complications from citrate infusion.** ***Conclusion:*** **Compared with controls, citrate clearance and metabolism in long-term hemodialysis patients is not impaired, and no significant acid-base disorder occurred during citrate anticoagulation. From these data, it is tempting to conclude that citrate anticoagulation can be used safely in patients with chronic renal failure on regular hemodialysis therapy. *Am J Kidney Dis* 46:903-907.**

INDEX WORDS: Hemodialysis (HD) therapy; anticoagulation; citrate; calcium; acid-base balance.

CITRATE ANTICOAGULATION is used increasingly in many hemodialysis units worldwide.[1,2] The advantage of this alternative anticoagulation is the strictly extracorporeal "regional" type of anticoagulation without impairment of coagulation within the body. Thus, bleeding complications related to anticoagulation cannot occur. Moreover, citrate provides a quality of anticoagulation superior to such conventional methods as unfractionated or fractionated heparin.[3] However, more than the quality of anticoagulation, an additional important mostly overseen point deserves attention: calcium is required not only for coagulation cascade, but also for activation of cellular elements of the blood, such as thrombocytes and leukocytes. Bohler et al[4] convincingly showed that during hemodialysis therapy using citrate anticoagulation, leukocyte activation and proteolytic enzyme release are suppressed. Recently, it was shown that cytokine release during hemodialysis[5] and leukocyte adhesion molecule expression also is mitigated when using citrate as anticoagulant.[6]

Thus, in patients at risk for bleeding, but also in subjects with heparin-induced thrombocytopenia, citrate presents an attractive method of anticoagulation. However, despite the increasing use of citrate anticoagulation, little is known about the impact of renal failure on citrate metabolism. In healthy subjects, citrate is metabolized to a substantial fraction in the kidney. Thus, impairment in metabolic kidney function, usually present in patients with terminal renal disease on hemodialysis therapy, also could affect citrate clearance.

However, it is not only the loss of metabolically active kidney mass that might impair citrate metabolism. It was shown in patients with chronic renal failure that accumulation of soluble toxins also can affect various metabolic pathways in such extrarenal tissues as the liver. Hepatic metabolism of gluconeogenetic intermediates and

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the tricarbonic acid cycle have been shown to be impaired in the uremic state.[7-10]

Thus, in this investigation, we evaluate citrate clearance during intravenous infusion of sodium citrate in patients with chronic renal failure on regular hemodialysis therapy with minimal residual function in comparison to subjects without renal disease.

METHODS

All subjects included in this study underwent immunoadsorption therapy using a standardized citrate anticoagulation protocol. Citrate kinetics were compared between patients with chronic renal failure on regular hemodialysis therapy and control subjects with normal renal function who underwent immunoadsorption therapy in an identical way.

Patients

Seven patients with chronic renal failure on hemodialysis therapy for at least 12 months were enrolled. These subjects had minimal residual function, with urinary output less than 400 mL/d.

Controls

Eleven subjects without impairment in renal function undergoing immunoadsorption therapy because of hyperlipidemia, myasthenia gravis, or multiple sclerosis served as controls.

Patients with diabetes mellitus type 1 or type 2 and those with liver disease were excluded from the study. Characteristics of patients with renal failure and controls enrolled are listed in Table 1.

Citrate Infusion

Citrate kinetics was evaluated during therapeutic apheresis therapy by using a standardized citrate anticoagulation protocol. All patients were administered ACD-A solution (Baxter, Munich, Germany; 1,000 mL containing 8.0 g of citric acid monohydrate [38 mmol/L], 22.0 g of disodium citrate dihydrate [81 mmol/L], and 24.5 g of glucose monohydrate [124 mmol/L]) for anticoagulation at a mean infusion rate of 5% of blood flow, corresponding to a mean citrate infusion rate of 0.33 mmol/kg/h. Calcium (0.5 mmol/mL) was infused into the venous port to maintain an ionized calcium concentration greater than 0.9 mmol/L within the systemic circulation.

Venous blood samples were obtained at baseline, during (20, 40, 60, 90, 120, and 180 minutes and at the end), and after (10, 20, 40, 60, 90, and 120 minutes) citrate infusion from the arterial needle. Citrate concentrations were measured by using a commercially available test kit (citrate-lyase UV method; R-Biopharm, Darmstadt, Germany). Total calcium was measured by means of a photometric test (Arsenaco 3 Method; Olympus, Tokyo, Japan), and blood gas samples were collected in a lithium heparin syringe and immediately processed by using blood gas analyzer ABL 700 (Radiometer Copenhagen, Brønshøj, Denmark) for ionized calcium, pH, bicarbonate, and base excess.

Pharmacokinetic Calculations

Pharmacokinetic analysis was performed by using computer software (Kinetica 3.0; Innaphase, Philadelphia, PA), and data were calculated by using noncompartmental approaches. Area under the concentration-time curve (AUC) values for plasma and interstitium were calculated from nonfitted data by using the linear trapezoidal rule. Volume of drug distribution (Vd) and total drug clearance (Cl) were calculated by use of standard formulae, as follows:

$$Vd = dose/(AUC * k_e)$$

$$Cl = k_e * Vd$$

where k_e is the elimination rate constant.

The half-life calculated for the terminal slope ($t_{1/2\beta}$) was calculated by means of the following equation:

$$t_{1/2\beta} = \ln(2)/k_e$$

The following parameters were determined: AUC, maximum concentration, and time to maximum concentration (Table 2).

Table 1. Clinical Characteristics and Baseline Laboratory Parameters of the Study Population

	Patients With Renal Failure (n = 7)	Control Group (n = 11)	*P*
Age (y)	40 ± 11	43 ± 18	0.75
Sex (male/female)	4/3	4/7	1.0
Weight (kg)	72 ± 16	71 ± 16	0.95
Creatinine (mg/dL)	9.6 ± 3.9	0.9 ± 0.2	<0.001
Blood urea nitrogen (mg/dL)	51.1 ± 25.3	11.9 ± 2.5	<0.001
pH	7.37 ± 0.02	7.4 ± 0.03	0.036
Standard bicarbonate (mEq/L)	21.5 ± 1.4	25.3 ± 1.5	0.013
Ionized calcium (mmol/L)	1.19 ± 0.16	1.07 ± 0.09	0.052
Aspartate aminotransferase (U/L)	19 ± 7	14 ± 8	0.39
Alanine aminotransferase (U/L)	13 ± 5	13 ± 9	0.94
Lactate dehydrogenase (U/L)	138 ± 43	168 ± 20	0.592

NOTE. Data expressed as mean ± SD. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; blood urea nitrogen in mg/dL to mmol/L, multiply by 0.357; bicarbonate in mEq/L to mmol/L, multiply by 1.