

Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients¹⁻³

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ABSTRACT

Background: Acute renal failure is a serious complication in critically ill patients and frequently requires renal replacement therapy, which alters trace element and vitamin metabolism.

Objective: The objective was to study trace element balances during continuous renal replacement therapy (CRRT) in intensive care patients.

Design: In a prospective randomized crossover trial, patients with acute renal failure received CRRT with either sodium bicarbonate (Bic) or sodium lactate (Lac) as a buffering agent over 2 consecutive 24-h periods. Copper, selenium, zinc, and thiamine were measured with highly sensitive analytic methods in plasma, replacement solutions, and effluent during 8-h periods. Balances were calculated as the difference between fluids administered and effluent losses and were compared with the recommended intakes (RI) from parenteral nutrition.

Results: Nineteen sessions were conducted in 11 patients aged 65 ± 10 y. Baseline plasma concentrations of copper were normal, whereas those of selenium and zinc were below reference ranges; glutathione peroxidase was in the lower range of normal. The replacement solutions contained no detectable copper, 0.01 μmol Se/L (Bic and Lac), and 1.42 (Bic) and 0.85 (Lac) μmol Zn/L. Micronutrients were detectable in all effluents, and losses were stable in each patient; no significant differences were found between the Bic and Lac groups. The 24-h balances were negative for selenium (−0.97 μmol, or 2 times the daily RI), copper (−6.54 μmol, or 0.3 times the daily RI), and thiamine (−4.12 mg, or 1.5 times the RI) and modestly positive for zinc (20.7 μmol, or 0.2 times the RI).

Conclusions: CRRT results in significant losses and negative balances of selenium, copper, and thiamine, which contribute to low plasma concentrations. Prolonged CRRT is likely to result in selenium and thiamine depletion despite supplementation at recommended amounts. *Am J Clin Nutr* 2004;80:410–6.

KEY WORDS Selenium, zinc, copper, thiamine, trace elements, balances, critical illness, acute renal failure, supplements

INTRODUCTION

Acute renal failure is a serious complication in critically ill patients and is associated with high mortality (1). Severe acute renal failure requires renal replacement therapy. Although controversial, continuous renal replacement therapy (CRRT) is frequently used in hemodynamically unstable patients in European centers (2). CRRT includes hemofiltration, which involves the

convection of fluids and solutes through a semipermeable membrane, and dialysis, which involves the diffusion of solutes through a low permeability membrane. The nutritional status of these patients is generally poor because of a combination of hypermetabolism, accelerated protein catabolism, and an altered response to nutritional support (3). Although the causes of malnutrition are many during acute and chronic renal failure, renal replacement therapy is likely to affect nutrition via 2 main mechanisms: 1) losses of nutrients through the filtration and dialysis processes, and 2) supply of substrates and other components with the replacement fluids (4). Indeed, depending on their composition, replacement solutions may constitute a source of carbohydrates, such as glucose and lactate. On the other hand, amino acids are lost in the effluent because of the permeability of the membranes; glucose is also lost when solutions without glucose are used. Other minerals are lost by the same mechanism, some on purpose, others not.

Trace elements are essential nutrients with regulatory, immunologic, and antioxidant functions resulting from their action as essential components or cofactors of enzymes (glutathione peroxidases and superoxide dismutase) throughout metabolism. Selenium and zinc metabolism have been shown to be altered in acute and chronic renal failure (5–9). The activity of plasma glutathione peroxidase (GSHPx), a selenoenzyme that is one of the most important antioxidants in the circulating compartment, has been shown to be depressed during renal replacement therapy (9, 10). This is probably due to the combination of a decreased synthesis by the renal parenchyma and to selenium deficiency. CRRT requires the use of large amounts of fluid containing physiologic amounts of some minerals and of buffers to promote acid-base homeostasis. The trace element content of these solutions is unknown: losses are likely to occur because the free trace elements are small in size and thus dialyze readily. Previous studies have investigated the importance of micronutrient losses

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during extra-renal replacement therapy. They have shown that selenium and zinc losses are negligible during peritoneal dialysis (11) and during renal replacement therapy (12). However, trace element balances are particularly difficult to carry out during CRRT because of the large volumes of replacement fluid (2–3 L/h) or dialysate that are required. The large volumes result in a significant dilution of minerals in the effluent solution, which makes trace elements extremely difficult to detect; major analytic efforts are required (13).

Vitamin status is also altered in patients requiring dialysis: plasma thiamine concentrations have been shown to be depressed during intermittent dialysis (14). This vitamin plays a key role in carbohydrate metabolism. Lactic acidosis, Wernicke-Korsakoff encephalopathy, and acute cardiac failure are classic manifestations of thiamine deficiency.

This study was designed to determine trace element and thiamine balances during continuous venovenous hemodiafiltration (CVVHDF) with the use of highly sensitive analytic methods and to compare the effects of 2 different replacement solutions, containing either sodium bicarbonate or sodium lactate as buffer.

SUBJECTS AND METHODS

The study was designed as a prospective randomized crossover trial. It was performed in the 17-bed surgical unit and the 14-bed medical intensive care unit (ICU) of the University Hospital, Lausanne, Switzerland, over a 22-mo period (2000–2001). Eleven critically ill adult patients were enrolled with approval of our institutional Medical Ethics Committee, and written informed consent was obtained from each patient or next of kin in accordance with the 1983 Helsinki Declaration. The inclusion criteria were as follows: ages 16–75 y, need for ICU treatment, diagnosis of acute renal failure requiring renal replacement therapy, and the failure of at least one other organ [on the basis of Sepsis-related Organ Failure Assessment scores; 15]. This assessment procedure considers 6 systems: respiratory, cardiovascular, renal, hepatic, coagulation, and neurologic. The exclusion criteria were as follows: absence of consent, blood lactate concentration >8 mmol/L, moribund state with survival beyond 48 h unlikely, acute liver failure (defined as severe cytolysis, factor V <30%, or liver encephalopathy), active hemorrhage preventing accurate metabolic determinations, and severe renal failure with preoperative creatinemia (creatinine >250 $\mu\text{mol/L}$) or chronic dialysis (local reference values: 45–106 $\mu\text{mol/L}$). Persons with moderate chronic renal failure, defined as a preoperative creatinine concentration of 130–250 $\mu\text{mol/L}$, were not excluded. The severity of illness on admission to the ICU was assessed on the basis of the Simplified Acute Physiology Score II (16).

Continuous venovenous hemodiafiltration

CVVHDF was performed with a Prisma machine (Gambro Renal Care Products, Lakewood, CO) according to a standard protocol. The filters (AN 69 membrane; Hospal, Lyon, France) and the replacement solutions [sodium lactate (Lac; Lactasol) and sodium bicarbonate (Bic; Hemosol B0), both from Hospal, Lyon, France] were changed 6 h before each 24-h protocol began to enable stabilization of the effluent composition after the change from Bic to Lac or vice versa. The dialysate flow rate was set at a 1000 mL/h, and the filtration rate was also set at a nominal flow rate of 1000 mL/h. Fluid balance, which was automatically regulated by the Prisma machine, was ordered by the ICU physician

TABLE 1
Composition of the replacement solutions¹

| | Bicarbonate solution ² | Lactate solution ³ |
|---|-----------------------------------|-------------------------------|
| Buffers (mmol/L) | | |
| Sodium bicarbonate | 32 | 0 |
| Sodium lactate | 3 | 40 |
| Copper ($\mu\text{mol/L}$) ⁴ | ND | ND |
| Selenium ($\mu\text{mol/L}$) | 0.01 | 0.01 |
| Zinc ($\mu\text{mol/L}$) | 1.42 | 0.85 |
| Thiamine (nmol/L) ⁵ | ND | ND |

¹ ND, not detected.

² Hemosol B0 (Hospal, Lyon, France).

³ Lactasol (Hospal).

⁴ Minimum detection: 0.02 $\mu\text{mol/L}$.

⁵ Minimum detection: 10 nmol/L.

according to the clinical requirements of the patients (24-h fluid balance was usually set at a range of –1000 mL to 1000 mL).

Study protocol

Each patient received 2 different replacement solutions containing Bic or Lac as a buffering agent in a randomized sequence over 2 consecutive 24-h periods (**Table 1**). Hemodynamic stability was required for validation of the study period (defined as a stable mean arterial pressure requiring no vasopressor change or intravenous fluid loading). The composition of the 2 solutions is shown in Table 1. Each study session lasted 8 h.

Measurements and sampling

Both replacement solutions were analyzed for micronutrients. All fluid inputs and outputs were recorded hourly. A plasma sample was collected at baseline and at the end of the session for measurement of albumin, C-reactive protein (CRP), trace elements, thiamine, and acid-base variables. Twenty milliliters of the effluent solution were collected every hour during the 8-h trial.

Nutritional support

The patients received artificial enteral or parenteral nutritional support. All patients received daily intravenous micronutrient supplements corresponding to recommended requirements during total parenteral nutrition (TPN) (17): 1 vial of multi-trace elements (Addamel N; Fresenius Kabi, Bad Homburg, Germany) containing 20 μmol (1.25 mg) Cu, 0.4 μmol (32 μg) Se, and 100 μmol (6.5 mg) Zn and 1 vial of multivitamins (Cernevit; Baxter AG, Volketswil, Switzerland) containing 3.5 mg thiamine. In addition, the patients received 100 mg thiamine (Benerva; Roche, Basel, Switzerland) intravenously to prevent deficiency during the first 48 h in the ICU.

Calculations

The CVVHDF micronutrient balances were calculated as the difference between the 8-h output in the effluent and the 8 h intakes resulting from the replacement solutions. The 24-h balance was calculated by multiplying this value by 3.

Analytic methods

Copper, zinc, and selenium in plasma and effluent were measured in duplicate by inductively coupled plasma mass spectrometry (Plasmaquad 3 ICP-MS; VG Elemental, Winsford, United

TABLE 2

Patient characteristics and therapy outcomes¹

| Subject no. | Age | Sex | Diagnosis | BMI <i>kg/m²</i> | SOFA | | | | Albumin <i>g/L</i> | CRP ² <i>mg/L</i> | Sequence of CRRT solution | Time in ICU before | | Outcome |
|-------------|-----|--------|---------------------------------------|--------------------------------|------|-------|----------|--------|-----------------------|---------------------------------|---------------------------------|-----------------------|-----------------------|---------|
| | | | | | SAPS | Score | Failures | CVVHDF | | | | LICU | | |
| 1 | 47 | M | Aortic valve surgery | 29.1 | 50 | 15 | 5 | 18 | 151 | Bic only | 1 | 53 | Survived | |
| 2 | 78 | M | Cardiac surgery, prior CRF | 25.8 | 52 | 10 | 5 | 18 | 200 | Bic only | 2 | 8 | Survived | |
| 3 | 77 | F | Abdominal aorta surgery, prior CRF | 28.3 | 52 | 17 | 6 | 18 | 231, 87 | Lac, Bic | 1 | 10 | Died | |
| 4 | 68 | F | Abdominal aorta surgery, prior CRF | 25.1 | 48 | 17 | 6 | 14 | 213, 105 | Lac, Bic | 2 | 24 | Survived | |
| 5 | 53 | M | Pulmonary embolism | 25.2 | 96 | 16 | 5 | 23 | 189 | Bic only | 1 | 6 | Died | |
| 6 | 55 | M | Abdominal aorta surgery, prior CRF | 32.4 | 43 | 12 | 4 | 24 | 241, 190 | Lac, Bic | 1 | 8 | Survived | |
| 7 | 59 | M | Abdominal sepsis | 28.3 | 31 | 8 | 3 | 16 | 94, 57 | Lac, Bic | 4 | 18 | Survived | |
| 8 | 72 | M | Cardiac surgery, prior CRF | 28.3 | 51 | 14 | 5 | 18 | 278, 174 | Bic, Lac | 3 | 28 | Died | |
| 9 | 66 | F | Septic shock | 24.8 | 77 | 19 | 6 | 17 | 181, 122 | Bic, Lac | 1 | 8 | Died | |
| 10 | 71 | M | Myocardial infarct | 32.0 | 76 | 17 | 5 | 17 | 249, 228 | Bic, Lac | 5 | 21 | Died | |
| 11 | 67 | M | Abdominal aorta surgery, prior CRF | 26.0 | 94 | 13 | 4 | 18 | 236, 154 | Bic, Lac | 1 | 14 | Died | |
| \bar{x} | 65 | 8M, 3F | — | 27.8 | 62 | 15 | 5 | 18 | 178 | 11 Bic, 8 Lac | 2 | 18 | 6 died, 5 survived | |

¹ SAPS, Simplified Acute Physiology Score; SOFA, sepsis-related Organ Failure Assessment score at initiation of the study; LICU, length of intensive care unit stay; CRF, moderate chronic renal failure; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; Bic, sodium bicarbonate; Lac, sodium lactate; CVVHDF, continuous venovenous hemodiafiltration.

² Where 2 values are given, the first value is for the solution used during the first session and the second value is for the solution used during the second session.

Kingdom) with the use of aqueous inorganic standards (18). All specimens were diluted in 1% nitric acid:0.2% *n*-butanol:0.2% *n*-propanol and 10 ppb indium as internal standard. The detection limits were 0.02 $\mu\text{mol/L}$ for copper, 0.08 $\mu\text{mol/L}$ for zinc, and 0.01 $\mu\text{mol/L}$ for selenium. The assays were linear to 24 $\mu\text{mol/L}$ for copper, to 23 $\mu\text{mol/L}$ for zinc, and to 1.9 $\mu\text{mol/L}$ for selenium. The accuracy (mean recovery from spiked samples) for each was as follows: 102% for copper, 102% for zinc, and 106% for selenium. The CV for all analyses was <3%. Plasma GSHPx was measured by the RANSEL method (Radox Laboratories, Belfast, United Kingdom). Erythrocyte and effluent thiamine concentrations were measured by HPLC with the use of thiamine pyrophosphate as standard (19). The HPLC method has an interbatch precision of 5.7% at a concentration of 223 nmol/L and a detection limit of 10 nmol/L. It is linear to 600 nmol/L. Albumin was measured colorimetrically (bromocresol green) and CRP by nephelometry.

Statistical analysis

The results are expressed as means \pm SDs. Micronutrient concentrations and effluent losses were compared by using two-factor repeated-measures analysis of variance for the effect of group (Bic or Lac) and time. Post hoc comparisons were made with Dunnett's or Scheffe's test as appropriate. Paired *t* tests were used to compare balances. Linear regression was used to analyze correlations between zinc in the replacement solution and in the effluent. Significance was set at a *P* value <0.05. The JMP statistical package (version 3.1.5; SAS Institute Inc, Cary, NC) was used for the analyses.

RESULTS

Eleven patients were enrolled. Their characteristics are shown in Table 2. Nineteen balance study periods were conducted,

including 11 Bic and 8 Lac sessions; 3 patients did not complete the lactate session (2 patients failed to receive the same solution throughout and 1 died unexpectedly from cardiac problems). All patients were mechanically ventilated and had multiple organ failure (≥ 2 organs other than the kidney); the median number of organ failures was 5 (Table 2). Six patients had previously experienced moderate chronic renal failure. Six patients died (55%) during their ICU stay, which agreed with the mortality expected on the basis of the Simplified Acute Physiology Score II.

CVVHDF was initiated within 2.0 ± 1.3 d in the ICU, and the first step of the investigation protocol was carried out after 5.5 ± 3.7 d in the unit. The CVVHDF was well tolerated: no side effects related to this therapy were observed during the study, except for isolated hyperlactatemia during lactate buffer infusion. The main CVVHDF variables (blood flow rates, filtration and dialysis rates, replacement fluid rates, and fluid balances) did not differ between the 2 measurement periods. The mean rate of replacement fluid delivery was 1710 ± 695 mL/h at the start of the 8-h period and was 1585 ± 450 mL/h at the end of the period. The mean amount of effluent measured was 1650 ± 630 mL/h at start of the trial and was 1670 ± 465 mL/h after 8 h.

Trace elements

Plasma

Baseline trace element concentrations were comparable with the 2 buffer regimens (Table 3). Plasma copper concentrations were within upper reference ranges, probably as a result of inflammation. Mean plasma selenium concentrations were below reference ranges; only 2 patients had concentrations within the normal range. Zinc concentrations were below the lowest reference ranges in all patients, reflecting, at least in part, a strong

TABLE 3Plasma and continuous venovenous hemodiafiltration variables at baseline and 8 h later at the end of the trial¹

| | Baseline (n = 11 Bic, 8 Lac) | 8 h (n = 11 Bic, 8 Lac) | Reference range |
|--------------------------------|---------------------------------|----------------------------|-----------------|
| Plasma | | | |
| Zinc ($\mu\text{mol/L}$) | 6.68 ± 0.66^2 | 6.10 ± 0.66^3 | 12.7–20.2 |
| Selenium ($\mu\text{mol/L}$) | 0.76 ± 0.20 | 0.71 ± 0.18^4 | 0.8–1.6 |
| Copper ($\mu\text{mol/L}$) | 19.52 ± 6.89 | 17.91 ± 6.21^5 | 12.5–21.0 |
| Glutathione peroxidase (U/L) | 660 ± 199 | 712 ± 403 | 425–1200 |
| Albumin (g/L) | 18 ± 3 | 17 ± 3 | 35–55 |
| Bicarbonate (mmol/L) | | | |
| Bic group | 24.7 ± 4.6 | 28.6 ± 6.1^4 | 23–27 |
| Lac group | 25.3 ± 5.1 | 30.4 ± 5.7^4 | |
| Lactate (mmol/L) | | | |
| Bic group | 2.00 ± 0.64 | 5.76 ± 2.39^4 | 0.6–2.4 |
| Lac group | 3.37 ± 1.15^6 | 7.96 ± 2.54^4 | |
| Erythrocyte thiamine (nmol/L) | 382 ± 109 | 264 ± 136 | 100–300 |

¹ Bic, sodium bicarbonate; Lac, sodium lactate. There was no time-by-treatment interaction.² $\bar{x} \pm \text{SD}$ (all such values).^{3,5} Nearly significantly different from baseline: ³ $P = 0.077$, ⁵ $P = 0.052$.⁴ Significantly different from baseline, $P \leq 0.001$.⁶ Significantly different from the Bic group, $P = 0.04$ (t test).

inflammatory response. A decrease in the concentrations of the 3 trace elements was observed between baseline and the end of the 8-h periods (significant only for selenium).

Replacement solutions

Both solutions contained significant amounts of zinc, with higher concentrations in the bicarbonate solutions (Table 1). Both solutions contained equally small quantities of selenium; copper was not measurable.

Effluent

Trace elements were detected in all effluent samples. Zinc concentrations in the effluent were lower than those in the replacement fluid (mean difference for the Bic and Lac sessions: $-0.52 \pm 0.39 \mu\text{mol/L}$). Selenium concentrations in the effluent were greater than those in the replacement fluid in all samples (mean difference for Bic and Lac sessions: $-0.026 \pm 0.019 \mu\text{mol/L}$). Trace element concentrations in the effluent differed between patients but were stable within patients during the 8-h

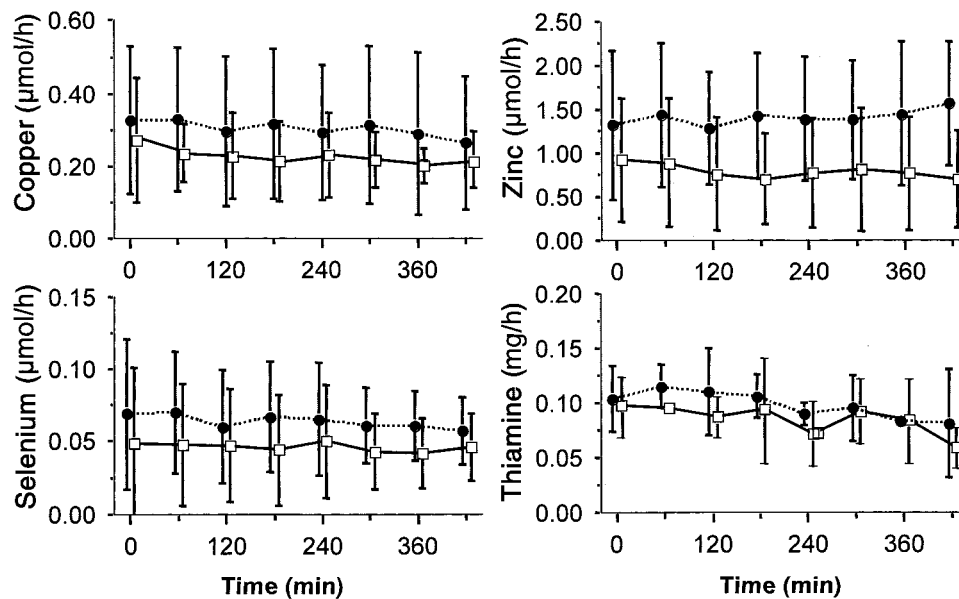


FIGURE 1. Mean (\pm SD) copper, selenium, zinc, and thiamine concentrations in effluents from patients with acute renal failure who received continuous renal replacement therapy (CRRT) with either sodium bicarbonate (Bic group; ●) or sodium lactate (Lac group; □) as a buffering agent. Zinc losses were significantly greater in the Bic group ($P < 0.0001$, two-factor ANOVA with post hoc Dunnett's test). No significant differences in copper, selenium, or thiamine were observed between the 2 groups, and there was no group \times time interaction for any of the 4 micronutrients.

TABLE 4Trace element and thiamine balances after 8 h of continuous venovenous hemodiafiltration¹

| | Copper ² | Selenium | Zinc | Thiamine ³ |
|---------------------------------------|---------------------|-------------------|--------------------|-----------------------|
| | μmol | μmol | μmol | mg |
| Fluid intake during 8 h | | | | |
| Bic group | ND | 0.14 ± 0.04^4 | 19.35 ± 6.11 | ND |
| Lac group | ND | 0.13 ± 0.04 | 11.28 ± 3.78 | ND |
| Both groups | ND | 0.13 ± 0.04 | 15.95 ± 6.56 | ND |
| Effluent during 8 h (measured hourly) | | | | |
| Bic group | 2.44 ± 1.55 | 0.52 ± 0.29 | 11.07 ± 5.61^5 | 1.46 ± 0.36 |
| Lac group | 1.82 ± 0.73 | 0.37 ± 0.08 | 6.30 ± 5.06^5 | 1.28 ± 0.34 |
| Both groups | 2.18 ± 1.28 | 0.46 ± 0.24 | 9.06 ± 5.77^5 | 1.37 ± 0.34 |
| 8-h Balances | | | | |
| Bic group | -2.44 ± 1.55 | -0.38 ± 0.28 | 8.29 ± 6.28^5 | -1.46 ± 0.36 |
| Lac group | -1.82 ± 0.73 | -0.24 ± 0.07 | 4.97 ± 4.36^5 | -1.28 ± 0.34 |
| Both groups | -2.18 ± 1.28 | -0.32 ± 0.23 | 6.89 ± 5.67^5 | -1.37 ± 0.34 |
| 24-h Balances | | | | |
| Bic group (μmol) | -7.32 | -1.15 | 24.86 | -4.39 |
| Lac group (μmol) | -5.46 | -0.71 | 14.92 | -3.85 |
| Both groups | | | | |
| (μmol) | -6.54 | -0.97 | 20.67 | — |
| (mg) | -0.41 | -0.077 | 1.34 | -4.12 |
| TPN dose (mg/d) | 1.2 | 0.035 | 6.5 | 2.5–3.5 |

¹ $n = 8$ in the Bic group and 8 in the Lac group. Note that the units for the 24-h balances differ from those for the other data. Bic, sodium bicarbonate; Lac, sodium lactate; ND, not detected; TPN, total parenteral nutrition.

² Minimum detection: $0.02 \mu\text{mol/L}$.

³ Minimum detection: 10 nmol/L .

⁴ $\bar{x} \pm \text{SD}$ (all such values).

⁵ Correlated significantly ($r^2 = 0.33$, $P < 0.0001$) with the amount of zinc in the replacement solution by linear regression.

study periods (**Figure 1**), which enabled extrapolation to 24 h. There were no significant differences in mean copper, selenium, and thiamine concentrations between the 2 sessions because of large interindividual variations, despite slightly higher mean values in the Bic sessions. Mean zinc losses were greater in the Bic sessions. CVVHDF balance data, including measured 8-h data and calculated 24-h balances, are shown in **Table 4**. The balances were slightly positive for zinc and were negative for copper and selenium.

Thiamine

Erythrocyte thiamine concentrations were available for 8 sessions only, because of technical difficulties. Concentrations were within reference ranges; the mean baseline value was $382 \pm 109 \text{ nmol/L}$. The amounts of thiamine detected in the effluent decreased over time (Figure 1). The mean balance in the Bic group was $-4.4 \pm 1.1 \text{ mg/24 h}$ and in the Lac group was $-3.4 \pm 1.4 \text{ mg/24 h}$ (NS).

Other variables

All patients had a strong inflammatory response, as reflected by an elevated CRP concentration ($178 \pm 60 \text{ mg/L}$) and a very low albumin concentration ($18 \pm 3 \text{ g/L}$) (Table 2). The low albumin concentrations were the combined result of dilution (fluid resuscitation), an intense inflammatory response, and a restrictive albumin infusion policy (no infusion if plasma albumin concentrations were $>15 \text{ g/L}$): these low concentrations were not significantly correlated with plasma zinc concentrations. The mean CRP concentration was positively correlated with plasma copper ($r^2 = 0.186$, $P = 0.024$). Mean plasma GSHPx concentrations (Table 3) were in the lower range ($660 \pm$

199 U/L); 5 values in 4 patients had concentrations below the reference range. Plasma GSHPx and selenium were positively correlated ($r^2 = 0.45$, $P < 0.0001$). The pH was similar in both sessions, with an initial mean pH value of 7.40 ± 0.08 in the Bic session and of 7.43 ± 0.12 in the Lac session. Baseline arterial lactate was higher after the 6 h of equilibration in the Lac group ($P = 0.004$). The bicarbonate and lactate blood concentrations increased as expected over time under the influence of the 2 buffer solutions.

DISCUSSION

The metabolism and status of micronutrients are altered in chronic renal failure; some of the abnormalities result from uremia, which can be further modified and exacerbated by dialysis procedures (20). The results of the current study show that status is also altered in acute renal failure because CRRT causes negative micronutrient balances as a result of continuous effluent losses. Copper, selenium, zinc, and thiamine were detectable in the effluent of all patients. Because these micronutrients are key elements in immune and antioxidant defenses (21), negative balances are likely to have deleterious biochemical and clinical consequences.

Trace elements

Selenium and zinc deficiencies are frequent in patients receiving chronic dialysis (5, 9). The current study showed that CRRT is associated with significant trace element losses in the effluent. These losses are important enough to threaten balances, especially if there is no systematic supplementation. The low selenium and zinc concentrations observed in our patients were caused by several

mechanisms, but mainly because of a strong inflammatory response with redistribution of trace elements from plasma to other tissues (17), mainly by dilution of the circulating compartment by resuscitation fluids, and because of inadequate intakes. Negative balances from dialysis will result in progressive deficiency and contribute to a further lowering of plasma concentrations. The low plasma concentrations observed in our trial agreed with those of another recent trial that included 8 ICU patients who required CRRT (12): compared with the healthy control subjects, the ICU patients had significantly lower blood concentrations of selenium, zinc, vitamin C, and vitamin E. The highly sensitive analytic methods used in our study explain why we were able to demonstrate significant micronutrient losses, which were either small or undetectable in the ultrafiltrate in Story et al's (12) study, except for copper, chromium, and vitamin C; chromium and vitamin C were not investigated in the current study. Because Story et al's study was not designed as a balance trial, the clinical significance of the low blood concentrations of selenium, zinc, vitamin C, and vitamin E in their critically ill patients remained unclear. We did indeed not measure all the intakes, nor all the losses (eg, feces, drains): we only considered the prescribed micronutrients and the quantities found in the effluent, most of which were clearly not in balance.

The trace element quantities lost in the effluent were stable over time in each patient (low within-patient variability), whereas the interpatient variability was large. The replacement solutions contained modest amounts of zinc but no measurable amounts of copper and only very small quantities of selenium. Because of the large amounts of fluids used during CVVHDF, the zinc contained in the solutions resulted in slightly positive zinc balances amounting to 20.4 $\mu\text{mol}/24\text{ h}$ (20% of a daily TPN dose). Copper balances were negative ($-6.5\ \mu\text{mol}/24\text{ h}$), a loss that corresponded to $\approx 30\%$ of a daily TPN supplement. The selenium losses were even more important; selenium balance was $-1.0\ \mu\text{mol}/24\text{ h}$, which is equivalent to 2.5 times that in TPN supplements. If prolonged, CVVHDF would thus cause selenium deficiency, despite the provision of intravenous supplementation in conjunction with enteral nutrition, a practice that is standard in our unit. In patients who do not receive TPN, micronutrients contained in enteral nutrition solutions are insufficient to compensate for such losses. The modest decrease in circulating trace element concentrations over the 8 h study period argues in favor of a depletion risk, which corroborates findings in patients receiving chronic dialysis (6–9).

The antioxidant status of patients with acute or chronic renal failure has been shown to be depressed, as reflected by low plasma concentrations of ascorbate, β -carotene, and selenium; low GSHPx activity; elevated MDA concentrations (22, 23); and low ceruloplasmin ferroxidase activity (24). The selenium status is particularly important to the antioxidant defense, because the activity of different glutathione peroxidases, which are selenoenzymes, decreases in selenium deficiency. GSHPx is one of the main antioxidants in the intra- and extracellular compartments. Depressed GSHPx activity has been shown in both chronic and acute renal failure (10). In the current study, mean plasma GSHPx concentrations were in the lower range; 4 of 11 patients had depressed activities and low plasma selenium concentrations. Plasma GSHPx and selenium were strongly correlated.

Thiamine


The current study also investigated acute thiamine changes, because thiamine metabolism has been shown to be altered in

patients undergoing intermittent dialysis (14). The mean thiamine losses were very high in our patients, amounting to $\approx 4\ \text{mg}/24\text{ h}$. The normal dietary recommendation of thiamine is $\approx 1.0\ \text{mg}/24\text{ h}$, and the total body thiamine content is usually accepted to be $\approx 30\ \text{mg}$. Body stores would be depleted in $\approx 1\ \text{wk}$ in the case of such persistent losses and no supplementation, which would put the patient at serious risk of deficiency. Thiamine is provided in intravenous nutrition solutions in various chemical forms: the recommended dietary allowances address thiamine as a single entity, whereas labels on multivitamin preparations list thiamine salts and thiamine equivalents. The intravenous supplements used in the current study provide 3.5 mg thiamine/d; another commonly used supplement (Soluvit N; Fresenius Kabi) contains 2.5 mg thiamine. In addition, our patients had received 100 mg thiamine during the first 48 h of their stay in our unit to replete their stores and to meet the increased requirements of critically ill patients (25). This systematic supplementation procedure may explain the normal mean thiamine concentrations observed in our subjects 5.5 d after ICU admission. However, recommended daily TPN supplements were not enough to meet the ongoing losses in CVVHDF. Moreover, such systematic supplementation in the absence of TPN is not a standard practice in all ICUs.

In patients with a preexisting thiamine depletion, negative balances may have deleterious consequences because thiamine is essential for glucose and lactate metabolism. Blood thiamine is frequently low in critically ill patients not receiving dialytic therapy; a very low concentration is associated with poor outcome (25), and additional losses will further compromise thiamine status. In a trial conducted in patients with chronic renal failure who were receiving intermittent dialysis therapy, plasma thiamine concentrations dropped to 75–82% of normal concentrations after each session. In patients supplemented with 1.5 or 8.0 mg thiamine, plasma concentrations returned to initial concentrations within 44 h. The authors concluded that daily thiamine supplementation in compliance with recommended dietary allowances is sufficient to keep thiamine status within the normal range during intermittent dialysis (14). The results of the current study indicate that usual thiamine supplementation doses are insufficient to substitute losses and hence to cover metabolic requirements during continuous dialysis. It is likely that all water-soluble vitamins are lost in a similar way in the effluent and that conventional supplements are insufficient in this condition.

Several trials have compared the metabolic effects of sodium lactate and bicarbonate as buffers for critically ill patients receiving CVVHDF. Conflicting results have been published concerning their respective metabolic merits, and there is no consensus regarding their utilization. We detected no significant differences in micronutrient balances or in plasma nutrient concentrations between the Bic and Lac groups.

In conclusion, CVVHDF caused negative selenium, copper, and thiamine balances in critically ill patients, regardless of the buffer solution used. Zinc balances were slightly positive, because of the presence of zinc in the replacement solutions used in our hospital. Nevertheless, because the zinc contents of the 2 buffer solutions (Bic and Lac) differed and because the patients were severely ill, as reflected by very low plasma albumin concentrations, additional zinc supplementation should be considered. The negative selenium balances were associated with low GSHPx activity, which suggests that the depressed plasma selenium concentrations reflected a deficiency and not just

redistribution as a result of a strong acute phase response. The effluent losses contributed to further alter the endogenous antioxidant defenses. The negative thiamine balances observed may also contribute to metabolic alterations in critically ill patients. CRRT may also result in the deficiencies of other water-soluble micronutrients not investigated in the current study. Although this life-saving technique may induce serious nutritional deficiencies of copper, zinc, selenium, and thiamine, these deficiencies can easily be remedied through the use of appropriate supplementation. 

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MMB designed the protocol, collected the data, helped perform the statistical evaluation, and helped write the manuscript. AS helped conceive the protocol, helped develop the analytic methods, supervised the laboratory analyses, and helped improve the manuscript. J-PR helped conceive the protocol, helped perform the statistical evaluation, and helped improve the manuscript. ER helped develop the analytic methods, performed most of the analytic work, and helped improve the manuscript. M-CC helped conceive the protocol, participated in the practical aspects of the sample collection, collected data, and helped assess the data. MB helped develop the analytic methods, helped with the analytic work, and helped improve the manuscript. RLC designed the protocol, participated in the statistical evaluation, and helped write the manuscript.

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