Trace Element Loss in Urine and Effluent Following Traumatic Injury

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Background: Few data are available to establish recommendations for trace element supplementation during critical illness. This study quantified the loss of several elements and assessed the adequacy of manganese and selenium in parenteral nutrition (PN). Methods: Men with traumatic injuries were grouped by renal status: adequate (POLY; n = 6), acute failure with continuous venovenous hemofiltration (CVVH; n = 2), or continuous venovenous hemodialfiltration (CVVHD; n = 4). PN supplied 300 µg/d manganese and 60 µg/d selenium. Urine and effluent (from artificial kidneys) were collected for 3 days and analyzed for boron, manganese, nickel, and silicon using inductively coupled plasma atomic emission spectrometry, and for selenium using atomic absorption spectrometry. Results: POLY manganese and selenium excretion averaged (standard deviation [SD]) 7.9 (3.3) µg/d and 103.5 (22.4) µg/d, respectively. All elements except selenium were detected in dialysate (prior to use). CVVHD effluent contained 3.5 and 7.3 times more manganese and nickel than CVVH ultrafiltrate, respectively. Loss of manganese averaged 2.6%, 21%, and 73% of PN amounts for POLY, CVVH, and CVVHD groups, respectively. Discussion: Minimal loss of manganese compared with the amount in PN suggests that excessive amounts are retained. POLY patients excreted more selenium than was in PN, indicating negative balance. POLY losses of boron and silicon were less than that published for healthy adults, reflecting less than typical intake, whereas loss during CVVH was in the normal reference range, possibly because of added intake from boron contamination of replacement fluids. All patients lost more nickel than amounts published for healthy adults. Conclusions: Current guidelines of 60-100 µg/d of parenteral manganese may be excessive for trauma patients. The uptake of manganese and nickel from contaminants in CVVHD dialysate should be investigated. (JPN Int Perent Enteral Nutr. 2008;32:129-139)

Keywords: acute renal failure; boron; manganese; nickel; trace elements; trauma; selenium; silicon

Severe traumatic injury evokes a hypercatabolic response and hypermetabolism that persist for weeks and frequently result in multiple organ system dysfunction. Such physiological stressors alter nutrient utilization and metabolism. The primary drivers of the stress response are blood-borne chemical mediators liberated from the site of injury. These cytokines stimulate release of growth hormones and stress hormones (e.g., glucagon) and cause the liver to increase its uptake and retention of some trace elements, particularly iron and zinc.1

Critically ill patients rely on nutrition support to meet requirements for energy substrate and essential nutrients. Parenteral nutrition (PN) is initiated in patients who do not tolerate enteral feeding or if access to the enteral route is inadequate. Injuries such as pelvic fracture with hematoma, massive GI resection, and mesenteric penetrating trauma (i.e., gunshot, stab wounds) often lead to prolonged GI ileus that may necessitate PN. Other conditions and procedures that can limit enteral feeding include acute pancreatitis and patient positioning (i.e., prolonged face down, supine, motion rotation).

Manganese and selenium are essential for life, and sufficient intake is critical for optimal recovery from traumatic injury.2-4 However, excess manganese can have toxic effects, some of which manifest as abnormal neurocognitive function.3
The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommends 60-100 μg/d of manganese and 20-60 μg/d of selenium as safe ranges for parenteral administration for generally healthy adults. A.S.P.E.N. noted that the requirements and tolerance of trace elements varies among individuals. Specifically, A.S.P.E.N. recommends reducing the dose of manganese for patients with hepatobiliary disease because manganese excretion may be impaired. Monitoring of serum manganese and other elements may be necessary for patients on long-term PN as well as others who are exposed to therapeutic formulations contaminated with trace elements. A.S.P.E.N. has made no recommendations for supplementing boron, nickel, or silicon because the necessity of these trace elements for humans has not been established. However, these elements are bioactive, and excess exposure (such as through contamination of medical pharmacotherapies) has the potential to lead to adverse effects.

The purpose of this study is to quantify daily urinary loss of manganese, selenium, boron, nickel, and silicon after traumatic injury. We also quantified the loss of these elements during continuous renal replacement therapy (CRRT). The loss of manganese and selenium was compared to the standard amount provided by PN to assess the nutrition adequacy of the PN solution to maintain trace element balance. The loss of manganese, selenium, boron, nickel, and silicon was compared with published reference values; substantially elevated values might indicate increased exposure from contaminated medical pharmacotherapies.

Materials and Methods

The protocol for this prospective, clinical observation of patients with traumatic injuries was approved by the institutional review board of the University of Maryland.

Subjects and Sample Collection

Male patients with traumatic injuries necessitating admission to an intensive care unit (ICU) at the R Adams Cowley Shock Trauma Center (Baltimore, MD) were eligible to participate if they required PN and urinary catheterization and their families provided informed consent. Patients were grouped by renal status: either adequate function (POLY; n = 6) or acute renal failure (ARF) with CRRT (n = 6) using continuous venovenous hemofiltration (CVVH) or hemodiafiltration (CVVHD). At the time of enrollment, CRRT patients were required to have blood urea nitrogen levels controlled in the range of 14.3-28.6 mmol/L (40-80 mg/dL), and POLY patients were required to have serum creatinine levels of ≤150 μmol/L (≤1.7 mg/dL) and urine output of at least 0.5 mL/kg per hour. The patient’s height and weight were reported by his family. No attempts were made to prospectively document or evaluate clinical signs of mineral deficiency or toxicity for the purpose of this study.

Any urine draining from the catheter was emptied hourly from the medical collection device (acute drain bag; Baxter, Deerfield, IL) into preweighed, trace element–free, 4-L sample containers (Fisher Scientific, Pittsburgh, PA) to produce three 24-hour pooled samples per patient.

For CRRT patients, effluent draining from the polyacrylonitrile artificial kidney filter (PAN03; ASAHI Medical Co, Tokyo, Japan) was emptied hourly into preweighed, trace element–free, 4-L sample containers (Fisher Scientific) for 72 consecutive hours. CVVH effluent represents 100% ultrafiltrate from the patient, whereas CVVHD effluent is a mixture of ultrafiltrate from the patient and spent dialysate. Standard medical protocols were followed to administer replacement fluid (postfilter) to help compensate for fluid and electrolyte losses during CRRT. After weighing each hourly collection of effluent and each 24-hour pooled urine collection, aliquot samples were drawn and acidified with 50 μL of trace element–free hydrochloric acid. When available, samples of dialysate were also collected.

Artificial Kidney In Vitro Study

To test for trace element contamination from the artificial kidney filter and the collection device, 0.9% normal saline was infused through the blood side of a new filter. Also, a typical dialysate solution (consisting of 0.9% normal saline with 25 mEq/L sodium bicarbonate) was infused through the side of the filter reserved for dialysate. Samples were collected prefilter and postfilter and from the collection device immediately after initiating fluid flow and again after 10 and 20 minutes.

Nutrient Management

Daily PN consisted of 500 mL of 10% lipid emulsion infused over 12 hours and a nutritional solution consisting of amino acids and dextrose with added electrolytes/minerals, vitamins, and trace elements infused at a constant rate over 24 hours. PN was formulated to provide a total of 126 kJ/kg (30 kcal/kg) and 1.5 g of protein per kilogram of body weight (preadmission weight) per day. Manganese (300 μg/d as sulfate) and selenium (60 μg/d as selenious acid) were added during compounding of PN.

Sample Preparation and Analyses

Effluent samples were thawed and mixed by vortex. A proportionate (1/1000 by weight) sample was pipetted from each hourly sample to create a composite 24-hour pooled
sample. The pooled samples were centrifuged at 3000 rpm for 10 minutes. The resulting supernatant was analyzed for boron, manganese, nickel, and silicon using an axial-viewed inductively coupled argon plasma atomic emission spectrometer (model Optima 3100 XL; Perkin Elmer, Norwalk, CT). Yttrium was added as an internal standard. Analytical accuracy was evaluated using lyophilized human reference urine (Seronorm Trace Elements in Urine; Nycomed Amersham Pharma AS, Oslo, Norway) certified to contain 12.9 (mean; range, 12.0-13.8) ng/L of manganese and 38.3 (36.5-40.1) ng/L of nickel. Laboratory analysis of the reference material yielded the following: 11.39 (11.38-11.40) ng/L of manganese and 37.8 (37.3-38.4) ng/L of nickel. An additional quality control standard solution was measured, and the coefficients of variation for the means (n = 7) of boron, manganese, nickel, and silicon were 2.8%, 1.7%, 3.2%, and 4.9%, respectively.

For selenium analyses, subject samples and the reference urine (Utah Laboratories, Inc, Valencia, CA) were prepared by pipetting 0.5 mL into 30 mL Pyrex beakers, into which was added 5 mL of 40% (wt/v) magnesium nitrate (Alfa/Aesar ACS grade), 5 mL of reagent-grade concentrated nitric acid, and 1 mL of reagent-grade concentrated hydrochloric acid. The beakers were covered with watch glasses and refluxed for 24 hours on hot plates at 100°C. Then, the watch glasses were removed, and the samples were heated until they had dried completely. They were then slowly heated in a muffle furnace to 450°C. To each was added 4 mL of 6 M hydrochloric acid (reagent grade) and distilled deionized water to achieve a total volume of 10 mL. The samples were analyzed using an atomic absorption spectrometer (model 5100PC; Perkin Elmer) equipped with a flow-injection system (FIMS-100) and an electrodeless discharge lamp for selenium with a detection limit of 0.10 ng/mL. Analysis of the reference urine, which was certified to contain 77.0 ng/mL (65.0-89.0 ng/mL) of selenium, yielded 74.6 ng/mL (68.9-79.5 ng/mL) of selenium. The coefficients of variation for the mean selenium of the reference urine and for a quality control standard solution of selenium were 7.1% (n = 3) and 1.1% (n = 8), respectively. Data are expressed as the mean (SD) or mean ± SEM.

### Subject Groups and Compliance With Protocols

Complete 24-hour urine collections were obtained for 3 consecutive days for 6 POLY patients. For 6 ARF patients, 2 were treated with CVH and 4 were treated with CVVH. A lack of PN support and/or prolonged interruption of CRRT resulted in some days of effluent collection being excluded from analysis. The following composites of effluent were analyzed for the CRRT group: patient CVVH-1, three 24-hour samples; patient CVH-2, one 24-hour sample; patient CVVH-3, two 24-hour samples; patient CVVH-4, one 24-hour sample; and patient CVVH-4, two 24-hour samples.

### Results

#### Subject Characteristics and Nutrition Support

The ages of subjects ranged from 18 to 62 years, and body weights ranged from 54 to 100 kg; there were no differences between POLY and CRRT groups in mean age or body mass index. On the day of admission, groups did not differ in severity of illness as measured by the Injury Severity Score (n = 12; mean, 32; range, 14-57), the Acute Physiology, Age, Chronic Health Evaluation III score (APACHE III; n = 12; mean = 39; range, 30-112), the multiple organ dysfunction score, or blood albumin concentration. All patients required mechanical ventilation at admission and throughout the study period. At the time of the study, groups did not differ in the number of days in the ICU since injury (range, 4-12 days), but scores for APACHE III were worse since admission for CRRT patients than for POLY patients, 123.6 ± 9.7 and 77.1 ± 9.1 (P < .03), respectively. Patients in the POLY group were polyuric (urine volume >2.5 L/d) on 1 or more study days. The energy and protein intake from PN did not differ between POLY and CRRT groups, and the mean values are listed in Table 1. All patients in the POLY group survived to be discharged from the hospital, whereas only 2 of the 6 CRRT patients survived (1 who had received CVVH and 1 who had received CVVH).

### Urine Concentration and Loss of Trace Elements After Traumatic Injury

For each POLY patient, day-to-day loss of urinary selenium was relatively consistent; coefficients of variation ranged from 4% to 17%. However, urinary loss of other
Table 2. Urine Concentration and Daily Loss of Trace Elements for POLY Patients\(^a\) Compared With Data Published for Healthy Volunteers

<table>
<thead>
<tr>
<th>Element</th>
<th>Concentration</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trauma Patients</td>
<td>Reference Population</td>
</tr>
<tr>
<td>Boron(^6,9)</td>
<td>ng/mL</td>
<td>mg/d</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.7 (40.7)</td>
<td>798 (geometric mean)</td>
</tr>
<tr>
<td>Range</td>
<td>31-135</td>
<td>398-1600 (confidence interval)</td>
</tr>
<tr>
<td>Manganese(^11,12)</td>
<td>ng/mL</td>
<td>µg/d</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.4 (0.8)</td>
<td>1.2</td>
</tr>
<tr>
<td>Range</td>
<td>1.8-4.0</td>
<td>&lt;0.2-3.3</td>
</tr>
<tr>
<td>Nickel(^13)</td>
<td>ng/mL</td>
<td>µg/d</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.0 (3.1)</td>
<td>1.1 (1.1)</td>
</tr>
<tr>
<td>Range</td>
<td>3.5-11.8</td>
<td>&lt;0.12-5.69</td>
</tr>
<tr>
<td>Selenium(^10)</td>
<td>ng/mL</td>
<td>µg/d</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>33.9 (5.4)</td>
<td>~30-40</td>
</tr>
<tr>
<td>Range</td>
<td>28.1-42.4</td>
<td>83.0-141.8</td>
</tr>
<tr>
<td>Silicon(^8)</td>
<td>ng/mL</td>
<td>mg/d</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5500 (2600)</td>
<td>5500 (2600)</td>
</tr>
<tr>
<td>Range</td>
<td>217-1013</td>
<td>~2525-14,000</td>
</tr>
</tbody>
</table>

\(^a\)POLY refers to adult male trauma patients with functioning kidneys (n = 6; 3-day average).

\(^b\)Newer instrumentation and greater precautions to protect samples from contamination have been used since 1980.\(^11\) Data published prior to 1980 may be higher than actual values due to contamination.

Trace elements exhibited greater variability for individual subjects. The coefficients of variation ranged 9%-49% for boron, 4%-61% for manganese, 12%-67% for nickel, and 7%-57% for silicon.

The urine concentration of trace elements and daily loss for the POLY group is compared to data from the literature for healthy volunteers in Table 2. For boron and silicon, the urine concentrations and total loss were less than that of reference populations.\(^6,9\) In contrast, the urinary selenium concentration was in the reference range; yet because of polyuria, daily loss of selenium was greater than that reported for healthy adults.\(^10\) For manganese and nickel, the urine concentration and daily excretion exceeded that of reference populations.\(^11,13\)

**Trace Element Contamination During CRRT**

Sufficient volumes of sample from the in vitro study to test contamination from a new artificial kidney filter were available only for analysis of selenium. Selenium was nondetectable in fluid samples that were collected preflow and postflow through the filter. Similarly, selenium was not detectable in normal saline or dialysate solutions, except for 1 sample consisting of 0.9% saline, 25 mEq/L sodium bicarbonate, 4 mEq/L potassium chloride, and 4 mEq/L of magnesium, which had a selenium concentration of 0.143 ng/mL. This level of contaminant in dialysate, if delivered over a 24-hour period, would have contributed only 3.1 µg/d to the effluent or 9% of the 35 µg/d average daily content of selenium measured in effluent from CVVHD patients.

In contrast to the results for selenium, all prefilter dialysate samples were contaminated with boron, manganese, nickel, and silicon (Table 3). These data suggest that contamination from manganese and nickel did not vary much from solution to solution, whereas the concentration of boron varied moderately and silicon varied even more markedly (and for reasons that were not readily apparent).

For 7 other dialysate samples not included in Table 3, nursing errors during preparation of dialysate led to excess concentrations of magnesium (14-33 mEq/L) compared with the prescription of 2 mEq/L. The use of this dialysate for 1 patient was associated with several
Table 3. Trace Element Concentrations in Normal Saline and Solutions Used for Dialysate

<table>
<thead>
<tr>
<th>Solution</th>
<th>n</th>
<th>Boron, ng/mL</th>
<th>Manganese, ng/mL</th>
<th>Nickel, ng/mL</th>
<th>Silicon, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl</td>
<td>2</td>
<td>5.96 (0.23-11.68)</td>
<td>1.80 (1.78-1.83)</td>
<td>4.27 (3.65-4.88)</td>
<td>30.75 (20.8-40.7)</td>
</tr>
<tr>
<td>0.9% NaCl, 25 mEq/L NaHCO₃</td>
<td>2</td>
<td>7.07 (6.21-7.92)</td>
<td>1.89 (1.93-1.94)</td>
<td>6.08 (5.64-6.52)</td>
<td>206.95 (151.45-262.45)</td>
</tr>
<tr>
<td>0.9% NaCl, 2 mEq/L KCl</td>
<td>1</td>
<td>BDL</td>
<td>1.84</td>
<td>3.06</td>
<td>1.18</td>
</tr>
<tr>
<td>0.9% NaCl, 2 mEq/L KCl, 1 mEq/L Mg</td>
<td>7</td>
<td>1.16 (0.09-3.65)</td>
<td>3.29 (2.49-5.93)</td>
<td>3.03 (2.51-3.44)</td>
<td>3.34 (0.10-9.87)</td>
</tr>
<tr>
<td>0.9% NaCl, 25 mEq/L NaHCO₃, 4 mEq/L KCl, 2 mEq/L Mg</td>
<td>2</td>
<td>3.36 (3.06-3.65)</td>
<td>3.94 (3.87-4.02)</td>
<td>1.64 (0.69-2.60)</td>
<td>25.70 (4.84-46.55)</td>
</tr>
<tr>
<td>0.9% NaCl, 25 mEq/L NaHCO₃, 3 mEq/L KCl, 3 mEq/L Mg</td>
<td>1</td>
<td>13.08</td>
<td>8.59</td>
<td>6.04</td>
<td>105.19</td>
</tr>
<tr>
<td>0.9% NaCl, 25 mEq/L NaHCO₃, 4 mEq/L KCl, 3 mEq/L Mg</td>
<td>1</td>
<td>8.74</td>
<td>6.26</td>
<td>6.79</td>
<td>70.02</td>
</tr>
<tr>
<td>0.9% NaCl, 25 mEq/L NaHCO₃, 4 mEq/L KCl, 4 mEq/L Mg</td>
<td>1</td>
<td>6.79</td>
<td>6.55</td>
<td>0.19</td>
<td>15.04</td>
</tr>
</tbody>
</table>

BDL, below detection limit; KCl, potassium chloride; Mg, magnesium; NaCl, sodium chloride; NaHCO₃, sodium bicarbonate. Selenium was not detectable in normal saline or dialysate solutions, except for 1 sample consisting of 0.9% NaCl, 25 mEq/L NaHCO₃, 4 mEq/L KCl, and 4 mEq/L of Mg, which had a selenium concentration of 0.143 ng/mL.

episodes of bradycardia, as previously reported,³ possibly because of mass transfer of magnesium from dialysate into the patient. The aberrant samples also had elevated concentrations of boron (26-40 ng/mL) and manganese (21-25 ng/mL), findings that supported previously published data that magnesium sulfate solutions used to compound PN are contaminated with boron and manganese.¹⁴⁶

The possibility of contamination of dialysate confounds the determination of trace element loss from CVVH patients. Hence, data from CVVHD were excluded from comparison to POLY patients.

Daily Loss of Trace Elements During CVVH Compared With POLY

The day-to-day variation in the loss of trace elements in ultrafiltrate was calculated for 1 CVVH patient (CVVH-1) for whom 3 days of ultrafiltrates were collected. The coefficients of variation were as follows: boron, 10%; manganese, 7%; nickel, 31%; silicon, 24%; and selenium, 88.6%. The high coefficient of variation for selenium resulted from a nondetectable amount (<0.10 ng/mL) in CVVH-1 ultrafiltrate on the first study day and 27 and 21 μg/d losses on the following days.

The urinary loss of trace elements by the POLY group is compared with the total loss in urine and effluent (ultrafiltrate) by the CVVH group in Table 4. The POLY and CVVH groups had overlapping ranges of selenium loss. In contrast, CVVH patients exhibited distinctly greater daily losses of boron, manganese, nickel, and silicon than excreted by POLY patients.

Discussion

Relatively few studies have investigated the requirements, status, or efficacy of supplementing trace elements during critical illness. Hence, few data are available for review by expert groups to establish trace element recommendations for these patients. In the first report of a 2-part investigation into mineral loss following traumatic injury, we described the loss of calcium, magnesium, and zinc in male trauma patients who required PN.⁵ In that study, patients who retained kidney function were able to conserve calcium by excreting less than normal amounts in urine. In contrast, ARF patients lost substantial amounts of calcium through the CRRT filter, and these amounts were not fully replaced by intravenous supplementation, which jeopardized blood calcium concentrations. The loss of zinc and magnesium increased after trauma, yet these losses could be offset by PN and bolus dose infusions of magnesium, yielding neutral or positive balance. We concluded that nutrition requirements to maintain blood concentration of calcium and magnesium during CRRT were greater than the amounts that had been provided by standard PN. The results presented in this article broaden our understanding of the disparity among various key trace elements in their response to traumatic injury.

Limitations and Benefits of Study Design and Methods

Trauma patients receiving PN represent a small, distinct subpopulation of critically ill patients. The use of PN presents an opportunity to definitively determine the amount
Table 4. Mean (SD) Urinary Loss of Trace Elements by the POLY Group Compared With the Total Loss in Urine and Effluent by the CVVH and CVVHD Groups

<table>
<thead>
<tr>
<th>Volume, L/d</th>
<th>Boron, mg/d</th>
<th>Manganese, µg/d</th>
<th>Nickel, µg/d</th>
<th>Selenium, µg/d</th>
<th>Silicon, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLY (n = 6) 24-h urinary loss</td>
<td>0.19 (0.09)</td>
<td>7.9 (3.3)</td>
<td>24.9 (10.0)</td>
<td>103.5 (22.4)</td>
<td>1.54 (0.77)</td>
</tr>
<tr>
<td>Urine 3.28 (1.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVVH (n = 2) 24-h effluent and urinary loss</td>
<td>1.50 (0.02)</td>
<td>62.7 (54.9)</td>
<td>133.7 (50.6)</td>
<td>51.7 (50.5)</td>
<td>12.26 (0.26)</td>
</tr>
<tr>
<td>Ultrafiltrate 33.11 (0.56)</td>
<td>1.58 (0.06)</td>
<td>64.0 (5.6)</td>
<td>140.0 (48.5)</td>
<td>N/A*</td>
<td>13.75 (0.86)</td>
</tr>
<tr>
<td>Total: urine 0.61 (0.35) and ultrafiltrate 33.11 (0.56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVVHD (n = 4) 24-h effluent and urinary loss</td>
<td>2.13 (1.21)</td>
<td>218.9 (168.6)</td>
<td>972.8 (1317.3)</td>
<td>35.2 (42.2)</td>
<td>16.21 (8.85)</td>
</tr>
<tr>
<td>Effluent (ultrafiltrate and spent dialysate) 49.84 (6.9)</td>
<td>2.14 (1.22)</td>
<td>219.4 (168.5)</td>
<td>973.8 (1316.7)</td>
<td>N/A*</td>
<td>16.31 (8.83)</td>
</tr>
<tr>
<td>Total: urine 0.19 (0.29) and effluent 49.84 (6.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodiafiltration; POLY, trauma patients with adequate renal function.

*Selenium analysis of effluent only; urine was not available (N/A) for analysis.

of nutrients entering the bloodstream (approximately 100% absorption). In contrast, during enteral feeding, the net amount absorbed by the patient is unknown unless stable isotope tracer studies are conducted. The amount of trace elements provided by PN and subsequently retained (not excreted) may differ from the amount retained from enteral nutrition. The results of this study may be relevant only for patients with a similar route and composition of feeding and severity of critical illness.

Because the amount of trace elements in urine can vary from day to day, our collection of all POLY urine over 3 days is a more reliable reflection of actual loss than would be obtained from collections of shorter duration, particularly spot samples. Only a small number of CRRT patients participated; therefore, results may be skewed and not accurately reflect the larger population of seriously ill CRRT patients.

**Boron**

POLY patients excreted less urinary boron (concentration and total) than amounts reported for healthy adults (Table 2).6,9,17 The lower loss is probably due to lower intake. Berner et al14 suggested that PN boron (from contamination) amounted to < 10% of what might be absorbed by adults from a typical oral diet. In our study, in addition to the calcium supplied in PN that may have been contaminated with boron, 1 POLY patient was administered 1 ampule (10 mL) of calcium gluconate, which may have supplied additional boron as contaminant.14,15 That day, urinary boron excretion was the highest of any POLY subject, 0.37 mg/d, compared with the subject's other 2 study days, for which the excretion was within the range of other POLY subjects (0.06-0.31 mg/d).

Boron has demonstrated beneficial effects related to bone metabolism in pigs and in vitamin D–deficient chicks and rats.18 It has been suggested that boron may enhance wound healing and modulate inflammatory response.19,20 Studies are needed to determine whether boron supplementation would be beneficial for humans recovering from traumatic injury.

**Manganese**

For POLY patients, the concentration of manganese in urine as well as the total urine output of manganese was increased above normal levels; typical output is approximately 1.0 µg/d.11,12,21 One potential explanation for increased losses might be an increased release of manganese from endogenous stores as a response to trauma. Another explanation might be PN supplementation at a rate in excess of the body's requirement. When we began enrollment in 1998, the American Medical Association had standing guidelines for administration of 150-800 µg/d of parenteral manganese to stable adults, and doses of 500 µg were commonly available in multi–trace element preparations for parenteral use.22 Moreover, high doses such as these were routinely used in practice.23 The 300 µg/d of PN manganese compounded by our pharmacy exceeded the current A.S.P.E.N. recommendation of 60-100 µg/d for adult patients with normal organ function.4 The daily loss of manganese by POLY patients represented only 3% of the amount in PN, indicating that IV infusion of 300 µg/d is excessive for most trauma patients and results in substantial positive balance. Moreover, our results suggest that amounts lower than the current A.S.P.E.N. guidelines would maintain positive manganese balance in critically ill trauma patients.

Individuals receiving excessive manganese, particularly those with compromised homeostatic mechanisms, have reported mild symptoms of headache and dizziness.24,25 Fitzgerald et al21 reported elevated red blood cell manganese in 2 patients receiving PN for acute pancreatitis
and in 15 patients supported with long-term PN in which 500 µg manganese were administered daily. Excessive exposure of laboratory animals and humans to manganese can lead to manganism, an accumulation of manganese in the central nervous system characterized by clinical features similar to those of idiopathic Parkinson disease.25-28 In a prospective study of human patients, Takagi et al27 demonstrated that whole-blood manganese concentration and the intensity of magnetic resonance imaging of the globus pallidus changed in response to the parenteral administration of 1099 µg/d of manganese, and these responses subsided after the therapy was discontinued. Lucchini et al29 reported that magnetic resonance imaging of manganese signals in the human brain was strongly associated with neurological symptoms exhibited by patients with chronic liver disease. This raises the question of whether some symptoms of liver disease may be secondary to increased retention of manganese that would normally have been secreted in bile and excreted in feces.

Evidence from animal studies is accruing to suggest that manganese distribution and accumulation in the body is related to interaction with iron. For example, rodent data suggest that iron deficiency and anemia may be risk factors for manganese accumulation and neurochemical alterations.30 Moreover, Miller et al31 suggested that manganese status may contribute to magnesium status. They found that after feeding pigs a deficient diet containing only 25% of the porcine dietary requirement for magnesium, the addition of manganese at 52 mg/kg of diet (a level approximately 2.5 times the amount thought needed during gestation and lactation) led to heart changes and sudden death. Thus, under conditions such as CRRT, in which the body loses substantial amounts of magnesium, insufficient replacement of this mineral may leave the patient particularly susceptible to adverse effects from excess manganese. Further research is needed to understand the mechanisms responsible for magnesium:manganese interactions.

The tolerable upper intake level (UL) of 11 mg/d of manganese for adults is based on human data of elevated blood manganese concentrations and neurotoxicity from consumption of contaminated water.3 Typically only a small percentage of dietary manganese is absorbed into the bloodstream, measured under experimental conditions to range from 1% to 9%. Thus, to translate the enteral UL to a maximum limit for absorption (IV infusion), 11 mg/d is multiplied by 1% and 9%; thus, the intended maximum for absorption by normal individuals who are capable of manganese excretion is likely within the range of 110-990 µg/d.

The patients in our study had abnormal gut function, lacked the stimulus for bile secretion that is triggered by enteral intake, and were not routinely defecating. Thus, they were unable to reduce body levels of manganese through the normal intestinal route. This raises concerns that trauma patients supported by PN may have increased retention and risk for toxicity from parenteral manganese, especially if currently recommended IV doses of 60-100 µg/d are administered for prolonged periods. Of additional concern is contamination or possible overage (ie, intentional addition of a greater quantity than the label claim) in trace element preparations for PN contributing unknown quantities of manganese greater than the amount prescribed. Pluhar-Murton et al32 measured manganese concentrations in trace element preparations for parenteral use that were higher than labeled amounts. They also detected manganese contamination of other components used to formulate PN, such as calcium gluconate, magnesium sulfate, and potassium chloride. Based on their analyses, they calculated that a 2-L bag of PN would contain 38 µg (6.7%) more manganese than the 560 µg expected of standard solutions in 1999. Studies should be undertaken to measure and monitor blood manganese concentrations of critically ill patients supported by PN containing manganese.

**Nickel**

The urine of POLY patients was 7 times more concentrated in nickel than reference levels (Table 2), and the total daily loss exceeded urinary excretion by healthy men.13,31,32

In humans, the lungs, thyroid, and adrenal glands accumulate relatively high concentrations of nickel (132-173 µg/kg dry weight, on average).33 Hence, high activity and turnover of this tissue and catabolism of other body tissues after trauma might have released nickel into circulation and contributed to the amount excreted. Such a mechanism is supported by reports that serum nickel concentration is elevated following cerebral stroke, thermal burns, myocardial infarction, and myocardial ischemia without infarction.34,35

Although provision of some dietary nickel has been shown to be beneficial for 17 animal species, including chickens, cow, goat, pig, rat, and sheep, nickel lacks evidence of essentiality for humans and is not intentionally added to PN.3,34 Yet nickel contamination of PN may have been a source of nickel. Berner et al34 reported nickel contamination in several components of PN, including magnesium sulfate and multivitamin preparations. In particular, they calculated that calcium gluconate, potassium phosphate, and sterile water might have contributed 70%, 10%, and 9%, respectively, to the 53 µg/d nickel detected in sample PN solutions. Ten years later, Pluhar-Murton et al32 were unable to detect a clinically relevant concentration (≥1 µg/L) of nickel in a PN solution. Thus, nickel contamination may have been greatly reduced by this time. However, a more likely
possibility is that the method of analysis used by Pluhotar-Murton et al.\textsuperscript{15} differed from that of Berner et al.\textsuperscript{14} for example, adjustment for sample content of NaCl, which can interfere with the analytical signal for nickel, may have affected the results.

Nickel is typically transported in the blood bound to albumin. However, trauma patients tend to be severely hypoalbuminemic, as was the case with our patients,\textsuperscript{5} so it could be hypothesized that the ratio of unbound to bound blood nickel might increase after traumatic injury, increasing renal filtration and loss.

The UL for oral consumption of soluble nickel salts was set at 1.0 mg/d for adults 19 years of age or older. The Institute of Medicine\textsuperscript{3} cautioned that individuals with preexisting kidney dysfunction are distinctly susceptible to the adverse effects of nickel exposure. The percentage of nickel absorbed from the diet is typically <10% but has been reported to range from 29% to 40% under experimental conditions.\textsuperscript{4} Thus, the enteral UL of 1.0 mg/d can be translated into an estimated maximum limit for absorption (IV infusion) by multiplying 1.0 mg/d by 10% to arrive at 100 μg/d absorption for normal individuals who are capable of urinary nickel excretion. Studies should be undertaken to measure and monitor blood nickel concentrations of critically ill patients and to verify whether PN and other medical pharmacotherapies represent sources of unintended exposure.

**Selenium**

Although urinary selenium concentrations for trauma patients were similar to concentrations reported for healthy individuals, our results must be examined in the context of polyuria and total daily loss. POLY patients lost more total selenium than reference amounts of 30-75 μg/d.\textsuperscript{39,36,35} The loss by trauma patients also exceeded the 60 μg/d amount in PN (averaging 173% of the amount in PN). These results reinforce findings by Berger et al.\textsuperscript{38} that urinary selenium losses are increased above normal during selenium supplementation after severe traumatic injury, although we report substantially greater losses of selenium. In that Swiss study, patients (n = 11) were infused daily with 62 μg selenium (0.8 μmol) during the first ICU week, and urinary selenium averaged 54 μg/d (SD, 21 μg/d; range, 16-140 μg/d). In addition, nonurinary selenium losses (averaging 15 μg/d) were measured. Although draining wounds (9 μg/d), bronchial and gastric aspirations (4 μg/d), and feces (2 μg/d) accounted for some loss, clearly urine excretion was the primary route of selenium loss in traumatically injured patients.

Our data confirm reports that crystalloid solutions used for blood volume expansion are not a clinically significant source of selenium.\textsuperscript{38-40} In contrast, components used to formulate PN, such as amino acid solutions, are contaminated with selenium. Pluhotar-Murton et al.\textsuperscript{15} calculated that a 2-L bag of their standard PN would contain 21 μg (31%) more selenium than the 67 μg expected (prescribed and labeled). Albumin solutions and blood products may also contain selenium.\textsuperscript{38}

Altered utilization of selenium and hypercatabolism of body stores are other potential contributing factors for increased loss in trauma patients. Hawker et al.\textsuperscript{40} determined that urinary selenium from non-supplemented critically ill patients in Australia was associated with urinary urea nitrogen excretion and was inversely related to nitrogen balance (r = -0.50, P < .01). They concluded that catabolic states were associated with increased selenium losses.

Baker et al.\textsuperscript{41} reported the reversal of selenium deficiency in a young adult on long-term PN by provision of 100 μg/d selenium. At the time of our study, A.S.P.E.N recommended administration of parenteral selenium in the range of 20-60 μg/d for adult patients who were receiving long-term PN.\textsuperscript{42} Today, 60 μg/d is the upper limit of safe daily dosing recommended for parenteral selenium for generally healthy adults.\textsuperscript{4} The amount of selenium required and tolerated during critical illness for patients with hypermetabolism and other stressors associated with the acute phase of traumatic injury has not been established. Avenell et al.\textsuperscript{43} reviewed 7 published randomized trials of selenium and ebselen (selenium-containing compound) supplementation on outcomes for critically ill adults. Based on a lack of effect reported for selenium supplementation on the number of days on a ventilator, length of stay in the ICU, total number of hospital days, and quality of life, they concluded that the evidence was insufficient to recommend supplementation. Heyland et al.\textsuperscript{44} also conducted a systematic review of the evidence for selenium alone as well as in combination with other antioxidant nutrients. Although selenium supplementation was not associated with a significant reduction in mortality (relative risk = 0.59, 95% confidence interval = 0.32-1.08, P = .09), they suggested nevertheless that critically ill patients might benefit from high-dose parenteral selenium.

The trauma patients in our study did not exhibit sufficient renal conservation of selenium to achieve selenium balance. A negative selenium balance might persist as long as the patient is in the hypermetabolic and hypercatabolic phase of recovery, accompanied by downsizing of the body pool of selenium and perhaps a lowered selenium requirement. Any greater selenium supplementation than what was administered in our study may not be retained during the first 2 weeks after injury. On the other hand, the relative safety of enteral selenium up to the UL of 400 μg/d (of which up to 390 μg/d might be absorbed)\textsuperscript{2} suggests that parenteral administration might be increased somewhat without an adverse effect for patients with adequate renal function.
Silicon

POLY patients excreted less urinary silicon (concentration and total) than amounts reported for healthy adults, which probably reflects low intake.\(^7,8,^{45}\)

Although essentiality has not been established for humans, some data suggest that low intake of silicon may be disadvantageous for collagen repair. Silicon status can alter collagen metabolism, affecting bone turnover in experimental animals. For example, choline-stabilized orthosilicic acid was reported to partially prevent femoral bone loss in aged ovariectomized rats compared with controls.\(^{46}\) This form of supplemental silicon was also reported to have positive effects on skin, nails, and hair in a randomized, double-blind, placebo-controlled study of 50 women whose facial skin had previously been damaged by overexposure to the sun.\(^{47}\) Also, Juguadoes on et al\(^{48}\) reported that silicon intake was correlated positively with bone mineral density at 4 hip sites in men and premenopausal women. Studies with animal models of traumatic injury are needed to determine whether silicon could promote recovery.

Considerations for CRRT

During CRRT, ARF patients lost substantially more boron, manganese, nickel, and silicon than POLY patients (Table 4). Increased losses by CVVH patients suggest they either had greater exposure (and greater blood concentration) than POLY patients and/or that POLY patients exhibited selective renal reabsorption and greater retention. In comparing CVVHD and CVVH, CVVHD effluent contained substantially more manganese and nickel than did CVVH effluent. The greater CVVHD measures suggest that dialysate and replacement fluids may be contaminated with trace elements.

In fact, boron contamination of IV calcium supplements has been reported.\(^14,^{15}\) The CRRT patients received substantial intravenous calcium every hour in replacement fluid (i.e., calcium gluconate or calcium chloride) to offset calcium loss in ultrafiltrate. For CVVH patients, up to 2 ampules (20 mL) of calcium gluconate was added per liter of replacement fluid, which averaged 31.7 L/d. Thus, a greater blood concentration of filterable boron via replacement fluid contamination might be one explanation for the 1.39 mg/d greater difference in boron output for the CVVH group compared with the POLY group. CVVH losses of boron were similar to that of healthy men (Table 2).\(^9\)

For CVVH patients, daily loss of manganese represented 21% of the 300 μg/d amount in PN, indicating the amount in PN is probably excessive during CRRT. The 24-hour effluent measures for manganese were even greater for CVVHD patients (Table 4). These findings suggest that dialysate might have been contaminated with manganese, with the caveat that only a small number of CRRT patients participated in this study and that individual differences may contribute to some of the variation in findings. Because the rate of dialysate flow through the filter (and into effluent) is typically 900 mL/h or 21.6 L/d, contamination of dialysate could contribute substantial amounts of trace elements to CVVHD effluent each day. The possible uptake of manganese from dialysate into the patient could pose a serious risk of exposure and should be investigated.

The 24-hour effluent losses for nickel were greater for CVVH patients than for CVVHD patients (Table 4). Among CVVH patients, the amount of nickel in effluent varied more than 10-fold, from 284 to 2948 μg/d. These losses were >2.5 times the estimated maximum limit for absorption for normal individuals (estimated from the UL as discussed earlier). These findings suggest that dialysate might have been contaminated with varying concentrations of nickel. If the concentration of nickel in dialysate exceeded the concentration in blood, it is possible that mass transfer (down the concentration gradient) could occur from the dialysate into the patient's blood. It is thus concerning that average concentrations of nickel measured in samples of dialysate (Table 3) substantially exceeded typical blood concentrations of healthy adults.\(^9,^{49,50}\) For CVVH patients, the possible uptake of nickel from dialysate during CVVH should be investigated, as this level of exposure could lead to adverse effects.

Selenium was not measured in the urine of CRRT patients, but the urine volume averaged only 332 mL/d (SD, 346 mL/d; range, 0-854 mL/d). The daily loss of selenium in ultrafiltrate during CVVH averaged 16 μg/d for 1 patient and 87 μg/d for the other patient, representing 27% and 145% of the prescribed amount in PN. Thus, these results suggest selenium losses and status may vary widely for individuals. During CVVHD, selenium loss appeared to be relatively unaffected by the use of dialysate, averaging 35.2 (±42.2) μg/d, which was within the range of loss of the CVVH patients. Selenium loss in our study was lower than the 382 μg/d estimated by Nakamura et al\(^{11}\) based on sieving coefficients of bovine blood, and lower than the 109 μg/d extrapolated by Berger et al\(^{52}\) from 8 hours of effluent samples (containing both dialysate and ultrafiltrate) from critically ill patients. As a group, our CRRT patients lost less selenium than POLY patients, whose loss ranged from 83.0 to 141.8 μg/d. Thus, selenium presents a different response to ARF/CRRT than the other trace elements examined. Further research is necessary to investigate selenium requirements and tolerance during CRRT, especially factors that may contribute to individual variation and how these factors change during recovery.

During CVVH, silicon losses increased more than those of POLY patients and were in the range of healthy men, whose urinary losses range from 4 to 32 mg/d.\(^7\) The difference in loss of silicon by POLY and CVVH patients
perhaps suggests increased exposure during CVVH, for example, by silicon contamination of replacement fluid and/or renal conservation by POLY patients.

In summary, the greater loss of trace elements during CVVH above the amounts lost by POLY patients may be due to one or both of the following factors: (1) trauma patients in ARF might have greater amounts of filterable boron, manganese, nickel, and silicon in circulation than other trauma patients, and (2) trauma patients with functioning kidneys reabsorb and retain the filtered boron, manganese, nickel, and silicon from the kidney tubule. Limited data for selenium loss during CVVH was too variable to reach conclusions regarding the adequacy of PN provision but suggest that selenium balance varies greatly among individuals. The possible uptake of manganese and nickel from dialysate during CVVHD is a possibility that should be investigated.

Conclusions

Manganese loss by all groups did not reach the amount provided by PN. The study participants were fed via PN because of impaired gut function and probably could not reduce body levels of manganese through normal mechanisms. This raises concerns of apparent increased retention and risk for toxicity of PN manganese by trauma patients. Of additional concern is the possible overage of manganese in trace element preparations for parenteral use and in contamination of parenteral fluids, resulting in administration of greater amounts of manganese than expected. Although current A.S.P.E.N. recommendations for IV doses of 60-100 µg/d are lower than the 300 µg/d amount administered in our study, they may also be excessive if administered for prolonged periods when biliary secretion and fecal excretion are impaired.

Data are accumulating that selenium loss in critically ill trauma patients is derived from several sources: catabolism of endogenous stores, PN, enteral supplementation, infused blood products, and therapeutic albumin solutions. The selenium requirement and optimal amount of supplementation to support recovery from traumatic injury are not known. Data from our study indicate that trauma patients do not conserve selenium during the acute phase of intensive care. Thus, intravenous doses greater than the current A.S.P.E.N. recommendations of 20-60 µg/d may not be retained. Whether increased dosing is beneficial could be further investigated.

Urinary losses of boron and silicon were low for the POLY group compared with loss via CVVH and compared with typical loss by healthy adults. Hence, these results may reflect lower exposure and renal conservation by POLY patients. All patients lost considerable amounts of nickel compared with typical loss by healthy adults, yet the source of this nickel and the implications of these losses are not known.

The greater amounts of trace elements measured in effluent from CVVHD compared with CVVH suggests that dialysate solutions are contaminated with trace elements, particularly with manganese, nickel, and silicon. In contrast, the daily amount of selenium in effluent does not appear to differ between these treatment modalities. These findings raise concerns that nickel and manganese contaminants might be sufficiently concentrated in dialysate to cross the semipermeable CVVHD membrane and enter the bloodstream. Uptake of manganese and nickel from dialysate during CVVHD should be prevented.

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