Zinc absorption in premature infants: comparison of two isotopic methods1-3

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ABSTRACT  The fractional absorption of an oral dose of zinc can be measured in adults when given simultaneously with an intravenous dose and subsequently measuring the ratio of the double isotopic enrichment of urine. To test this method in very-low-birth-weight (VLBW) premature infants \( n = 5 \) females and 7 males, \( 1160 \pm 290 \text{ g} \) (\( \bar{x} \pm \text{SD} \)) birth weight, \( 29 \pm 4 \text{ wk gestational age} \), an oral dose of either 300 or 1200 \( \mu g \cdot 68Zn \cdot kg^{-1} \cdot d^{-1} \) was equilibrated with formula or human milk and administered simultaneously with either 50 or 100 \( \mu g \cdot 70Zn \cdot kg^{-1} \cdot d^{-1} \) given intravenously \( 35 \pm 3 \text{ wk postconception}. \) Urine and fecal samples were collected for \( 3-6 \text{ d} \) and analyzed by inductively coupled plasma mass spectrometry. Endogenous fecal zinc (EFZ) was determined from isotopic enrichment, whereas net absorption and retention were calculated by traditional methods. The mean fractional absorption calculated from urine was \( 0.22 \pm 0.09 \) and from feces it was \( 0.25 \pm 0.07 \). Zinc intake averaged \( 1821 \pm 330 \text{, fecal excretion} \), 1637 \( \pm 419 \), and urinary excretion 67 \( \pm 30 \mu g \cdot kg^{-1} \cdot d^{-1} \). EFZ averaged 390 \( \pm 270 \mu g \cdot kg^{-1} \cdot d^{-1} \) and ranged from 48 to 889 \( \mu g \cdot kg^{-1} \cdot d^{-1} \). Net absorption was 220 \( \pm 316 \mu g \cdot kg^{-1} \cdot d^{-1} \) and net retention was 131 \( \pm 334 \mu g \cdot kg^{-1} \cdot d^{-1} \). True absorption was 373 \( \pm 161 \mu g \cdot kg^{-1} \cdot d^{-1} \). Fecal collection is difficult, tedious, and often incomplete, and may be replaced by urine collection for the fractional absorption of zinc in groups of premature infants.  


KEY WORDS  Zinc absorption, premature infants, stable zinc isotopes

INTRODUCTION

Zinc is an essential trace element required by humans for growth, immune function, smell, taste, wound healing, and cognitive development (1, 2). The bioavailability of zinc, expressed as zinc fractional absorption, can be calculated as the difference between the mass of an isotopic dose administered orally and the mass of the subsequent tracer excreted in the feces divided by the mass of the original dose (3, 4). Previously, we showed using stable isotopes of zinc that the absorption of an oral dose of \( 68Zn \) can be measured in adults when it is given simultaneously with an intravenous dose of \( 70Zn \) and the ratio of the isotopic enrichment of urine is subsequently measured (5). We found that this method makes it easier to measure fractional absorption in adults than do current techniques requiring long fecal collection periods and/or multiple venipunctures (6, 7). This method could be advantageous for assessing zinc absorption in premature infants. It is particularly important to know the absorption of oral zinc for these infants who have a high requirement for zinc because of their low stores at birth, rapid growth rate, and potentially high losses of zinc into the gut (8-10).

Therefore, the purposes of this study were to compare the fractional absorption of zinc measured by fecal enrichment with the fractional absorption of zinc measured by urine isotopic enrichment, and to use this data as well as data derived from traditional balance procedures to assess zinc balance and endogenous excretion of zinc in premature infants.

SUBJECTS AND METHODS

Subjects

Twelve infants weighing <1500 g at birth (\( \bar{x} \pm \text{SD} \): 1160 \( \pm 290 \text{ g} \)) with a gestational age of 29 \( \pm 4 \text{ wk} \) were recruited from the Dr Charles Janeway Child Health Centre and the Grace General Hospital, St John’s, Newfoundland, Canada. The protocol was approved by the Hospital and University ethics committee and parental consent was obtained for each infant. The gestational age of the infants was determined from the last menstrual period of the mother as well as by the method of Dubowitz et al (11). If there was a discrepancy of >2 wk between the two assessments, the latter was used. Size for gestational age was defined as appropriate if the birth weight fell within 2 SDs of the weight for gestational age according to the growth curves of Lubchenco et al (12). Infants were clinically stable and on full oral feeds (no hyperalimentation) for \( \geq 3 \text{ d} \) before isotope administration. Infants were gavage-fed either a formula for premature infants—Similac Special Care (Ross Laboratories, Columbus, OH) or Enfamil (Mead Johnson Inc, Norfolk, VA)—or their own mother’s breast milk (Table 1) with added Human Milk Fortifier (Mead Johnson Inc). Both formulas were low in iron and contained medium-chain triacylglycerols (MCTs) as the fat source.

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**ZINC ABSORPTION IN PREMATURE INFANTS**

TABLE 1
Characteristics of the 12 infants in the study

| Infants fed Special Care formula | 10 |
| Infants fed breast milk | 2 |
| Birth weight (kg) | 1.16 ± 0.29 |
| Gestational age (wk) | 29.3 ± 4.0 |
| Postnatal age at study (d) | 38 ± 23 |
| Weight at study start (kg) | 1.60 ± 0.25 |
| Weight gain during study (g) | 21.1 ± 8 |
| Intake of milk (mL · kg⁻¹· d⁻¹) | 162 ± 22 |
| Urine output (mL · kg⁻¹· d⁻¹) | 60 ± 15 |
| Total dry fecal weight (g) | 40 ± 21 (12–63) |
| Time until first feces (h) | 18 ± 21 (0.5–64) |

1 n = 5F, 7M.
2 Ross Laboratories, Columbus, OH.
3 One female and one male.
4 ± SD. 
5 Range.
6 From the time of isotope administration.

**Preparation and administration of isotopes**

In the present study, trace element-free hydrochloric acid (Baker Scientific, Toronto, Canada) and subboiling distilled nitric acid were used throughout. High-purity distilled deionized water (> 18 MΩ/cm) was obtained by passing distilled water through a deionization system (Barnstead Co, Boston). The weighing of samples, addition of reagents, and drying or evaporation were performed in a clean laboratory with laminar-flow benches.

Zinc isotopes (⁶⁸Zn and ⁷⁰Zn) with various enrichments were obtained as zinc oxide from the Stable Isotope Division of Oak Ridge National Laboratory (Oak Ridge, TN) and from a Russian source (Atomergic Chemets Corp, New York) as shown in Table 2. Enriched isotopes were dissolved in a few drops of 6 mol HCl/L and diluted either in high-purity water (oral ⁶⁸Zn isotope) or saline solution (intravenous ⁷⁰Zn isotope). After the pH was adjusted to 6, the solutions were passed through a 0.2-μm filter and stored in sterile glass vials until delivery. Before use, each vial was checked for purity from pyrogens with the Limulus Amebocyte Lysate Test Kit (Whittaker Bioproducts, Walkersville, MD).

The oral doses of zinc (either 300 or 1200 μg · kg⁻¹· d⁻¹) were equilibrated overnight with an individual milk feed (30–75 mL) and were chosen to examine the effect of low and high quantities of zinc on ion absorption in a concurrent experiment. The doses were administered alternately to infants as they entered the study. Baseline fecal, urine, and blood samples were collected before isotope administration. The infants were given the intravenous dose (either 50 or 100 μg · kg⁻¹· d⁻¹) in a scalp vein over a 5-min period with a butterfly syringe that had been flushed with saline solution. Immediately afterward, the milk feed enriched with the oral dose was given directly into the stomach by nasogastric tube, which had already been in place as part of normal infant care. A small portion of enriched milk was saved for isotopic analysis. Bottles and milk were weighed before and after delivery to measure the amount of milk given. Infants were placed on a metabolic bed for the duration of the study (14).

**Sample collection**

From the time the doses were administered, all urine and fecal samples were collected for 4 ± 1 d (range: 3–6 d) by using a modified metabolic bed. Urine was collected in either 12-h (infants 1–9) or 8-h (infants 10–12) pools. Infants 10–12 had shorter urine collection periods to increase the number of urinary enrichment measurements. Fecal samples were collected on ashless filter paper as passed, and then placed in acid-washed polypyrrole containers. The urine samples were collected via a syringe from the pan under the metabolic bed. Any regurgitated material was collected on ashless filter papers. Fecal, regurgitated, and urine samples were stored at −20 °C until analyzed. Quantities of feeds consumed during the studies were recorded from hospital charts.

We defined the balance period as the time from when the administration of the isotopes began until the time when the last urine sample was collected. Each balance period included excretion of stool and urinary collection, representing 3–6 d of intake. We aimed for 4-d collections to encompass total excretion of the unabsorbed oral isotope in these infants (15, 16); however, the study length depended on the health of the child and the willingness of parents and staff to continue. The intake period was defined as the intake of zinc from 24 h before the isotope administration until 24 h before the final urine collection, ie, balance = intake – excretion. Zinc intake was calculated as all zinc received during the balance period, including the zinc from formula and the oral dose. The intravenous dose was not included because it contributed < 2% of the total daily intake. We used a 24-h lag time between intake and excretion because that was the average time that it took for the first feces to be passed after administration of the isotope, as also reported by others (15, 16).

Weight gain was calculated as the average weight gain during the balance period. Postconceptional age was defined as the time from conception (in wk) to the start of the study. Postnatal age was the time from birth (in d) to the start of the study.

**Digestion procedure**

The volume of each urine collection was measured and urine was transferred into glass beakers that contained two to three glass beads to prevent overboiling. One milliliter of concentrated HNO₃ was added to each 10 mL urine followed by 1.0 mL H₂O₂ to break down any recalcitrant lipid materials.
Samples were then dried on a hot plate until a gummy residue remained, ashed at 450 °C for 24 h, and then dissolved in 6 mol HCl/L to a volume of 10 mL (5, 17).

Frozen fecal samples were allowed to thaw at room temperature and were then homogenized by stirring with a 20-cm nonmetal propeller until a slurry was formed, and freeze-dried. Approximately 0.5 g freeze-dried feces was placed in a glass beaker containing two to three glass beads followed by the addition of 2 mL HNO3 and 1.0 mL H2O2. The samples were then dried, ashed at 450 °C for ≥ 24 h, and dissolved in 6 mol HCl/L to a volume of 25 mL. Regurgitation samples were treated similarly.

Preconcentration of zinc

Before they were used, empty columns (~12-mL Poly-Prep column, Bio-Rad 731-1550; Bio-Rad Laboratories, Hercules, CA) were cleaned in 5% HNO3 for 2 d followed by another 2 d in high-purity water. A slurry of AG 1-X2 anion exchange resin (chloride form, 100–200 mesh, reagent grade; Bio-Rad Laboratories) was added to the column and cleaned with successive rinses of 12, 6, 4, and 0.5 mol HCl/L with water added between each acid rinse. To separate zinc from the other trace elements, digested urine and feces dissolved in 6 mol HCl/L were applied to 1.0 mL resin (urine) or 2 mL resin (feces). Trace elements other than zinc were removed with subsequent gradients of HCl and zinc was collected in 0.5 mol HCl/L (18). This last eluent was evaporated and then brought up to 20 mL in 0.1 mol HNO3/L as a 1-mg/L solution in preparation for analysis by inductively coupled plasma mass spectrometry (ICP-MS). Ratios of 65Zn to 64Zn and 70Zn to 69Zn were determined with an Elan 250 ICP-MS (SCIEX, Thornhill, Canada) (17). Poisson counting statistics ranged from 0.26% to 0.43% for 70Zn, 64Zn and 0.06% to 0.34% for 69Zn,68Zn in feces and from 0.25% to 0.51% for 70Zn,64Zn and 0.06% to 0.08% for 68Zn,66Zn in urine samples, giving a value ≤ 1% for our samples, which was within the range of precision reported for this method (17). Total zinc was measured by flame atomic absorption spectrophotometry (AAS) using standardized procedures. AAS data for intravenous and oral isotopic doses were corrected to account for the variations in average atomic mass due to the isotopic composition of the enriched materials (Table 2).

Calculations

Using isotopic data we calculated the fractional absorption of the oral zinc dose for urine samples according to the method of Yergey et al (19) using the following formula:

\[
\text{Fractional absorption of zinc in urine} = \frac{(\% E) \text{ oral} \text{ (intravenous dose)}}{(\% E) \text{ intravenous} \text{ (oral dose)}}
\]  

(1)

where %E is percentage isotopic enrichment, which is calculated from the isotopic ratio of the sample. Isotopic enrichment is defined as the amount of zinc in the sample from an isotopically enriched source divided by the total amount of zinc in the sample (20). The formula for fractional absorption of urine is independent of both the concentration of zinc (total zinc) in the sample and volume of urine. The fractional absorption of urine reported for each infant represents the mean fractional absorption of urine determined from the last five (subjects 1–9) or six (subjects 10–12) urine collections. For subject 7, only the last three urine collections were used because of the shorter collection period of 3 d.

For subjects 7–12, isotope (70Zn) from a Russian source was given as the intravenous isotope. This intravenous preparation contained 11.20% 68Zn, the same isotope that was given orally (Table 2). By taking all these isotope contributions and their relation to each other into account, enrichment of 68Zn from the oral dose appearing in the urine was corrected for the effect of the 68Zn contributed by the intravenous dose with the use of simultaneous equations before determining fractional absorption in the above equation (21).

For feces, fractional absorption was determined by subtracting the cumulative fraction of the oral dose recovered in the feces from 1. The cumulative fecal excretion of the isotope is defined as the mass of the total oral isotope recovered in feces divided by the mass of the oral dose (16).

Fractional absorption of zinc feces

\[ = 1 – \text{fraction of isotopic oral dose recovered in feces} \]  

(2)

Fecal excretion of the oral isotope was adjusted for the resecretion of absorbed oral isotope by using standardized procedures (16).

Fecal endogenous loss of zinc (EFZ) was estimated by using the following formula:

\[ \text{EFZ} = \frac{(\text{ECR} \times \text{EIV})}{(\text{MIV} \times \text{days})} \]  

(3)

where ECR refers to the total zinc in an individual fecal sample and EIV is the enrichment of 70Zn in that sample. The products of this calculation for all individual samples collected during the measurement period are summed and divided by MIV, the average 70Zn enrichment in the last five (for subjects 1–9) or six (subjects 10–12) urine samples times the length of the collection period in days (22). True absorption was calculated from the fractional absorption of urine and the average daily zinc intake during the study.

Using traditional techniques, we calculated net absorption as the difference between dietary intake and fecal excretion of unlabeled zinc during the balance period. Net retention of zinc was calculated as the difference between the total dietary zinc intake and the sum of unlabeled zinc in urine and fecal excretions during the balance period (15).

Statistical analyses

Statistical analyses were performed by using SPSSx (23). The fractional absorption of urine reported for each infant represents the mean fractional absorption of those urine samples that fell within the 95% CI. Paired t tests were carried out between the fractional absorption of urine and that of feces for each subject; t tests were carried out to assess differences between sex and size for gestational age. Correlation tests were also performed to evaluate the degree of association between fractional absorption, other zinc indexes, and the characteristics of study subjects, and between the fractional absorption of urine and that of feces. To further assess the agreement between these two methods, the comparison of Bland and Altman (24) was performed. Statistical significance for all tests was set at P < 0.05.
RESULTS

Subjects

Characteristics of the infants are shown in Table 1. Ten subjects were formula-fed and two infants were fed human milk. Four additional infants were studied; however, their data are not included because their fecal collections were incomplete. All infants were maintained on normal feeds throughout the study. There were no differences in any study variables according to gestational age; therefore, data for the 12 subjects were pooled.

Fractional absorption

We calculated the absorption of zinc by comparing the urinary enrichment of an orally administered isotope with that of a second isotope given intravenously. Examples of urinary enrichment data for both the oral and intravenous isotopes are presented in Figure 1 for subject 1. Each point in Figure 1 represents one urine collection from this infant, and therefore no error bar is presented. The enrichment of urine with the intravenous isotope reached its maximum in the first 24 h. The enrichment in urine with the oral isotope reached its maximum, on average for all infants, beyond 24 h. The ratio of the enrichment of intravenous and oral isotopes in urine stabilized, in general, at or after 40 h for all infants. The mean fractional absorption of urine and feces was 0.22 ± 0.09 and 0.25 ± 0.07 (r = 0.5, P = 0.13; NS), respectively (Table 3). The limits of agreement, as defined by Bland and Altman (24), between urinary and fecal fractional absorption indicated that fractional absorption of feces could be either 0.15 below or 0.12 above the fractional absorption of urine. There were no differences in the fractional absorption of urine or zinc according to sex or size for gestational age. The fractional absorption of urine was inversely correlated with birth weight (r = -0.7), gestational age (r = -0.7), and weight on the study day (r = -0.8). The fractional absorption of urine was also inversely correlated with the size of the oral dose (r = -0.75). The amount of fecal 70Zn recovered as a percentage of the original dose of 70Zn given intravenously was 5.11 ± 2%.

Zinc balance

Complete zinc balance data for 12 subjects are shown in Table 3. Net retention and net absorption of zinc were positive on average, except for two infants. Values for EFZ were 390 ± 270 μg·kg⁻¹·d⁻¹ as calculated according to Krebs et al (22).

![Graph of isotope enrichment](https://example.com/graph.png)

FIGURE 1. Isotope enrichment of intravenous (iv) and oral tracers in the urine of a formula-fed infant (subject 1).

<p>| TABLE 3 |</p>
<table>
<thead>
<tr>
<th>Zinc balance data and fractional absorption for fecal and urinary collections from 12 infants</th>
</tr>
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<tbody>
<tr>
<td>Value</td>
</tr>
<tr>
<td>Zinc intake (μg·kg⁻¹·d⁻¹)</td>
</tr>
<tr>
<td>Fecal excretion (μg·kg⁻¹·d⁻¹)</td>
</tr>
<tr>
<td>Urinary excretion (μg·kg⁻¹·d⁻¹)</td>
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<tr>
<td>Net retention</td>
</tr>
<tr>
<td>(μg·kg⁻¹·d⁻¹) (%)</td>
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<tr>
<td>Net absorption</td>
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<tr>
<td>(μg·kg⁻¹·d⁻¹) (%)</td>
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<tr>
<td>True absorption (μg·kg⁻¹·d⁻¹)²</td>
</tr>
<tr>
<td>EFZ (μg·kg⁻¹·d⁻¹)¹</td>
</tr>
<tr>
<td>Fractional absorption (fraction of oral dose)</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>Feces</td>
</tr>
</tbody>
</table>

¹ As a percentage of total zinc intake during the balance period.
² Calculated from fractional absorption.
³ Endogenous fecal loss of zinc.

EFZ was inversely correlated with birth weight (r = -0.74) but not with study length.

DISCUSSION

The urinary and fecal appearance of zinc isotopes after simultaneous intravenous and oral administration was determined by using ICP-MS based on the dual isotope work pioneered by Yergey et al (25) for calcium. Once the slopes of the isotopic disappearance in urine decline in a proportional manner (Figure 1), it is possible to calculate the fractional absorption of urine. The time at which the fractional absorption of urine plateaued, ≥ 40 h, was the same as that in a similar study of zinc enrichment in four normal adults (5). This finding suggests that the handling of zinc by the kidney was not influenced by age or body size. Further, we expected the isotopic zinc fed in the manner prepared in this study to be as well absorbed as that of intrinsic zinc (26).

Fecal and urinary measures of fractional absorption are two different independent measures of zinc absorption during the same time period. Fecal and urinary fractional absorption in the same subjects were in good agreement for 8 of 12 subjects; however, the group means for the two methods were very similar (fractional absorption of feces = 0.25 ± 0.07; fractional absorption of urine = 0.22 ± 0.09). Further, only for the fractional absorption of urine was there an inverse relation between the size of the oral dose and fractional absorption. This suggests that the urine method may be more accurate than the fecal isotopic method because one would expect absorption to vary inversely with the size of the dose (27) and in adults is the method of choice for measuring zinc absorption (28). Nonrandom collection errors and irregularities in fecal excretion tend to overestimate both absorption and retention (15) and we observed higher values for the fractional absorption of feces in 8 of 12 subjects. These errors may explain the apparent high fecal absorption seen for subject 10 (fractional absorption of feces = 0.26; fractional absorption of urine = 0.12). In contrast, subject 7, who had a higher urinary absorption (fractional
absorption of feces = 0.24; fractional absorption of urine = 0.36), had only a 3-d urine collection. Perhaps a longer collection period would have resulted in more similar results between urine and feces.

Data from the analysis of Bland and Altman (24) suggest that fecal data are more likely to underestimate absorption than are urinary data and indicate variation between the two methods. We believe that a larger study than the one performed here is required to more properly compare these two methods and to explain differences in individual results.

From this data, the determination of zinc absorption in groups of premature infants by fecal monitoring can be replaced by monitoring the double isotope enrichment of urine. The advantage of this method is that only a single venipuncture is required to administer the intravenous dose and an estimate of fractional absorption can be determined from several points. The method is less invasive and obtrusive for the infant and less time consuming for the staff than is the collection of multiple blood and/or fecal samples.

Difficulties with the urine-collection method include possible contamination of urine with oral isotope from stool, leading to elevated estimations of absorption and increased variability in the fractional absorption of urine, particularly when urine and feces are collected simultaneously. Although we recommend collection of a 24-h urine sample, our results suggest that an 8-h urine sample should give an approximate estimate of fractional absorption in this population, as has been suggested for calcium absorption (25). This sample must be collected after the stabilization of the enrichment ratio, or at least 40 h after isotope administration.

By combining data from isotopic enrichment of feces and urine and nonisotopic measurements of zinc intake and excretion, we were able to examine the zinc status of premature infants. However, note that the isotopic dose comprised ≈28% of the daily intake and as such was outside the physiologic range of zinc intake examined in the following studies.

Most infants in our study were in positive zinc balance over the study period and had similar weight gains (21 ± 8 g Zn · kg⁻¹ · d⁻¹). Two of 12 infants were in negative balance, which is in keeping with results reported for infants of a similar age (34 ± 2 wk) (6, 15). One of those infants was the lightest (1100 g) and youngest (29 wk) at the time of the study. This negative balance occurred even though all of our study infants were receiving recommended intakes of zinc (10). It is known that breast-fed infants absorb more zinc than do non-breast-fed infants (14), and indeed our two breast-fed infants had the highest true absorption (486 and 885 μg · kg⁻¹ · d⁻¹).

Some, but not all premature infants appear to have excessive zinc losses through the intestinal route (6, 9, 15). We found that two infants were in negative net zinc retention and at least three others had excessive EFZ (600–900 μg · kg⁻¹ · d⁻¹) relative to mean daily intakes (1821 ± 330 μg · kg⁻¹ · d⁻¹). These endogenous losses are considerably higher than those reported for full-term infants by Krebs et al (22) and Ziegler et al (27)—≈35 μg · kg⁻¹ · d⁻¹—but were similar to data from Ehrenkranz et al (14)—454 ± 351 μg · kg⁻¹ · d⁻¹. Infants in that study had a gestational age (30 ± 2 wk at birth and 32 ± 2 wk at time of study) similar to our study infants and received the same type of infant formulas, which supplied 12 mg Zn/L, as did our study infants. These results occurred because of increased endogenous zinc excretion in response to increased zinc intake (29). Dauncey et al (6) and others (14, 30) found that zinc balance was likely only to be positive at 36 wk postconceptional age and that zinc absorption correlated with postconceptional age. They suggest that improvement in zinc balance occurs with gut maturity because of a reduction in zinc losses into the gastrointestinal tract.

Voyer et al (31) showed that premature infants of 32 wk postconceptional age could be in positive zinc balance when fed MCTs in their formula. All formula-fed infants in our study consumed formula containing MCT oils; however, 2 of 12 infants still were not able to maintain positive balance. Net absorption (total zinc intake − total zinc excreted in feces = 220 ± 316 μg · kg⁻¹ · d⁻¹) corresponded to values reported by others (6, 15, 30, 32) but was lower than that (670 ± 400 μg · kg⁻¹ · d⁻¹) reported by Tyrralla (33). The average net retention of zinc in our study infants (131 ± 334 μg · kg⁻¹ · d⁻¹) fell short of the 250 μg · kg⁻¹ · d⁻¹ estimated by Shaw (34) to be that amount needed between 24 and 36 wk to meet tissue requirements. Low retention of zinc occurred despite intakes in our study that were considerably greater than those of Dauncey et al (6) and Serfass et al (26) and similar to those of others (15, 35).

In conclusion, zinc absorption measured by urinary enrichment of stable isotopes can be used to assess the fractional absorption of an oral dose in groups of premature infants. According to our data, before 36 wk postconceptional age, some premature infants will lose zinc from body stores regardless of intake, so that a good source of zinc is important once the gut matures.

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