Zinc and micronutrient supplements for children1,2

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ABSTRACT    Provision of zinc supplements to children should be considered when their usual diet is low in absorbable zinc; severe stunting, low plasma zinc, or both; or persistent diarrhea. Inadequate zinc intakes are highly prevalent in developing countries, especially during the period of complementary feeding when zinc requirements are high and breast milk contributes little. To date, systematic evaluation of the acceptability of different zinc salts used as supplements is lacking. Some zinc salts are unpalatable and cause problems, such as nausea, at higher doses. Zinc carbonate and oxide are insoluble and poorly absorbed. Little information on the bioavailability of different zinc supplements in the presence of dietary inhibitors of zinc absorption exists. More information is needed on the quantity and frequency of dosing. Consideration should be given to the routine inclusion of zinc in iron supplements provided to children and to the simultaneous inclusion of other micronutrients in zinc supplements. Am J Clin Nutr 1998;68(suppl):495S–8S.

KEY WORDS    Zinc, iron, supplements, children, preschoolers, phytate, complementary feeding, developing countries

INTRODUCTION

Supplementation of children with zinc, or with zinc in conjunction with other micronutrients, may be beneficial in some situations. These include the following: a diet that is low in animal products and based on high-phytate cereals and legumes, especially during the period of complementary feeding; severe growth stunting, low plasma zinc concentrations, or both; and episodes of persistent diarrhea. Supplements may be particularly justifiable during relatively short periods of special vulnerability to zinc depletion, such as pregnancy and early childhood.

ADEQUACY OF CHILDREN'S DIETARY ZINC

Animal products are usually the best source of dietary zinc, in terms of both content and bioavailability. Because diets in developing countries are predominantly based on plants and often high in phytates, which inhibit zinc absorption strongly, it can be difficult for children in these countries to obtain their recommended intake of zinc from their usual diet. For example, in the Nutrition Collaborative Research Support Program (CRSP) sponsored by the US Agency for International Development, the predicted prevalence of preschoolers with intakes of zinc inadequate to meet basal requirements (ie, to prevent deficiency symptoms) was 57% in Kenya, 25% in Mexico, and 10% in Egypt (1). The prevalence of intakes inadequate to meet the preschoolers' normative requirements for zinc (ie, allowing for storage) was 90%, 68% and 36%, respectively, in the 3 countries. The higher prevalence of inadequacy in Kenya and Mexico was due to diets high in phytate (from maize and beans) and low in animal products. A subsequent zinc supplementation trial in children of similar age from the same Mexican community reduced morbidity from diarrhea but did not improve growth (2). In other developing countries, low intakes of zinc and high dietary phytate to zinc ratios were reported for older children (3). As discussed by Gibson and Ferguson (4) elsewhere in this supplement, it is possible to increase the amount of zinc absorbed from plant-based diets but this usually requires changes in food selection, preparation, and availability that may not always be feasible.

ZINC AS A SPECIAL PROBLEM DURING COMPLEMENTARY FEEDING

Breast milk does not supply an abundant amount of zinc. The growth velocity of breast-fed infants was reported to increase with zinc supplementation even in North America (5) and France (6), although more research is certainly needed to verify whether this and other benefits result from providing zinc supplements to breast-fed infants.

It can be difficult to meet the zinc requirements of infants and young children during the period of transition from milk to solid foods. We examined this question in a recent review of complementary feeding (7). The approach was first to estimate the zinc intakes of children between 6 and 24 mo of age by using published values for usual breast milk consumption by age and the zinc content of breast milk. The zinc needed from complementary foods was then calculated as the difference between zinc requirements (estimated to be 2.8 mg/d for 6–24 mo of age) and zinc intake from breast milk. From these calculations it can be seen that complementary foods must provide 84–89% of the zinc required by infants between 6 and 24 mo of age. On the basis of the average intake of breast milk in developing countries, an infant 6–9 mo of age would need to consume 50–70 g liver or lean beef/f, or ~40 g dry fish, to provide the additional zinc required from complementary foods. These analyses, and our examination of zinc intakes of infants and young children in Peru

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and Mexico, suggest that many infants and young children in developing countries are unlikely to meet their zinc requirements from food, and that zinc supplementation or fortification may be especially useful during this period of life.

FORMS OF ZINC SUPPLEMENTS

Considerations affecting the decision about the method of providing zinc supplements include solubility, bioavailability, taste, side effects, cost, and required frequency of dosing. Information on the form and dosage of zinc was available from our meta-analysis of trials that evaluated the effect of zinc supplements on growth (8). In the 25 trials, most investigators (n = 15) used zinc sulfate. Other forms were zinc acetate (in 3 studies, typically more recently); zinc gluconate (in 2 studies); amino acid chelates including zinc methionine (in 2 studies); and zinc carbonate, chloride and oxide (one study each). There was no relation between supplement type and growth response, but this may have been due to the small number of trials with each form of zinc. In 18 trials of the effect of zinc supplementation on morbidity, most investigators used zinc sulfate (n = 6) or acetate (n = 7).

An informal survey of investigators who conducted zinc supplementation trials revealed that there was usually little basis for their choice of one form of supplement over another. However, one investigator reported that the taste of zinc citrate was unacceptable in an amount supplying only 3 mg Zn, even when given in orange juice. A solution of zinc methionine supplying 20 mg Zn has a sulfurful taste that can be disguised by adding sugar, citric acid, and citrus flavor. Zinc sulfate and gluconate were stated to have an acceptable taste at the doses used (10–20 mg). Nausea and cramping occur when 50 mg Zn is provided to adults as a single dose of zinc sulfate (9–11). In one report there is a comment that zinc acetate, given daily in dosages of 25–50 mg 3 times/d to prevent copper accumulation in patients with Wilson disease, causes less dyspepsia than the same amount of zinc given as zinc sulfate (11). A systematic evaluation of the acceptability of available zinc supplements to consumers is needed.

The relative solubility of zinc salts in aqueous solution varies widely: zinc sulfate and chloride are very soluble, zinc acetate is freely soluble, and zinc carbonate and oxide are practically insoluble (12). Solubility in aqueous solution should be strongly related to absorbability. This would explain why zinc absorption from the carbonate salt was significantly lower than from the sulfate or acetate salts, as assessed by postconsumption plasma zinc concentrations (13). By using a similar approach, zinc was determined to be absorbed similarly from acetate and sulfate salts, but poorly from the oxide salt (14). Thus, zinc carbonate and zinc oxide are poor choices for zinc supplementation in humans. Gastric pH is also an important determinant of solubility because there may be some conversion of insoluble zinc salts to zinc chloride in the presence of gastric acid. Henderson et al (11) reported that at low intragastric pH (≤3) postdose plasma zinc concentration (area under the curve for 8 h) was 40% higher for zinc acetate supplements than for zinc oxide. However, under conditions of higher intragastric pH (≥5), zinc absorption from zinc acetate was reduced by 28% and that from zinc oxide was reduced by 82%. Some investigators measuring zinc absorption in metabolic studies administered zinc supplements in orange juice or a cola drink to improve solubility of the zinc. Poorer solubility with higher pH may be a factor to consider in populations in which gastric atrophy and achlorhydria are more prevalent because of infections from bacteria such as Helicobacter pylori. Henderson et al also revealed that a single 50-mg dose of zinc as acetate produced nausea and vomiting in 5 of 10 subjects when intragastric pH was ≤3 and in 7 subjects when the pH was ≥5; the mean duration of nausea was 40 min and on average it started 80 min after the zinc dose (11). Fewer subjects reported problems with zinc oxide (20% at pH ≤3 and 10% at pH ≥5), presumably because it was less soluble. Interestingly, many of the zinc supplements available in the United States are in the form of zinc oxide (11), probably because it is inexpensive.

Little information exists on the bioavailability of supplemental zinc when consumed in conjunction with food containing inhibitors of zinc absorption such as phytate; for iron, however, many studies revealed that the bioavailability of soluble iron supplements consumed with food is similar to that of dietary iron, i.e., absorption is affected similarly by dietary constituents. It is relatively easy to investigate the bioavailability of iron by measuring the amount of isotopically labeled oral iron that becomes incorporated into erythrocytes. Measurement of zinc bioavailability is more difficult. One approach used in humans is the postdose increment in plasma zinc (9, 15, 16). Unfortunately, postprandial plasma zinc values are greatly reduced and zinc absorption is delayed as a result of meal feeding (17–20), so this approach is not valid for comparisons among supplements consumed in the presence of food. Moreover, the postprandial decline in plasma zinc is related to zinc status, with a greater decline occurring after a period of zinc restriction (21). High doses of zinc (≥25 mg) are required for changes to be detected in measurements of urinary zinc (9), and zinc excretion is affected by consumption of sucrose (22), protein (23), and some amino acids that bind zinc (24). Some animal bioassays may be useful for assessing the relative bioavailability of various zinc supplements from different diets. For example, a chick bioassay showed that when consumed in corn-soybean or soy-isolate diets, zinc from zinc methionine was twice as available as zinc from zinc sulfate, but there was little difference when both forms of zinc were consumed in a pure amino acid diet (25). Rats have intestinal phytase activity that limits their validity for these types of studies.

Satisfactory approaches for evaluating the bioavailability of zinc supplements from human diets include the dual stable-isotope method proposed by Friel et al (26) and measuring whole-body retention of radioactive zinc 10–14 d after a test meal (27). A whole-gut lavage technique was also developed (28). Extrinsically added zinc isotopes were absorbed similarly to those used to intrinsically label milk-based formula diets in humans (29), but rat studies showed that extrinsically added isotopes may not exchange fully with endogenous zinc in many foods (30). Zinc chelates such as zinc methionine may need to be intrinsically labeled if the extrinsic label is not exchangeable with the chelated zinc.

Research is also needed on the relative efficacy of different frequencies and doses of zinc supplements. Between 5 and 20 mg Zn/d was administered in most studies of the effect of zinc on growth; in our meta-analysis of these studies supplements ranged from 1.5 to 50 mg/d (x; SD ± 13). The approximate efficiency of absorption of zinc from aqueous solutions is 60% for 5 mg, 50% for 10 mg, and 40% for 15 mg (31), such that a greater amount is absorbed from higher doses if consumed in the absence of a meal. In the presence of meals, however, absorption
appears to be saturated when intake reaches ≈5 mg/meal, with 1 mg Zn being absorbed, probably because the exogenous zinc has to compete for absorption with endogenous zinc secreted in response to the meal (32, 33). When a zinc supplement is distributed among 3–4 meals/d, saturation probably occurs at a total intake of 10–12.5 mg/d, with ≈5–6.5 mg absorbed (31). This implies that distributing zinc over the day’s meals can result in a substantially greater total amount of zinc being absorbed. If, as it has been suggested (34), once-weekly supplementation with iron is as effective as daily iron supplementation, it is important to establish whether weekly administration of zinc will produce significant improvements in zinc status, enabling the two nutrients to be administered simultaneously.

The World Health Organization (35) has proposed safe upper limits of zinc intake by children as follows: for 0.5–1 y of age, 13 mg/d; for 1–6 y of age, 23 mg/d; and for 10–12 y of age, 32 and 34 mg/d, respectively, for girls and boys. Effects on copper status may be seen below these intakes.

**COMBINING ZINC WITH OTHER MICRONUTRIENTS IN SUPPLEMENTS**

As discussed above, breast milk provides only a small percentage of the iron and zinc requirements of infants after 6 mo of age in developing countries. For children aged 18–30 mo included in the Nutrition Crisp, the predicted prevalence of inadequate intakes of absorbable iron was higher than that of absorbable zinc except in Kenya, where more ascorbic acid was consumed (1). Although none of the preschoolers in Egypt, Kenya, or Mexico were predicted to have inadequate copper intakes, it may be prudent to include copper in zinc supplements because of the well-established inhibitory effect of zinc on copper absorption.

Diets that provide inadequate amounts of zinc are likely to provide inadequate amounts of iron as well, because meats and fish are the best sources of both nutrients. In addition, parasites such as hookworm will cause losses of both of these nutrients in fecal blood. Thus, with the possible exception of illnesses such as diarrhea in which zinc losses are higher than those of iron, it is reasonable to assume that many children suffer from deficiencies of both nutrients simultaneously. Because iron supplements are often provided for infants and young children, it is logistically feasible to add zinc to these supplements. Of a solution containing 10 mg Zn and 25 mg Fe/mL, 0.5 mL would supply the child’s requirement for both zinc and iron. Provided in these quantities and ratio, the iron is unlikely to inhibit zinc absorption (36) or precipitate copper deficiency. The United Nations Children’s Fund is conducting a multisite trial to evaluate the benefits of adding zinc to iron supplements. Although the age at which supplemental iron is most needed (around 6–24 mo for breast-fed infants) corresponds to the age when zinc is also difficult to obtain from the diet, one limitation of dual supplementation may be that zinc stores could become depleted relatively soon after supplements are withdrawn, in contrast with iron stores, that are likely to last for some years.

Iron and zinc deficiencies are likely to be accompanied by deficiencies of other micronutrients, such as vitamin A, when usual diets are of poor quality with low intake of animal products and when parasites and infections contribute to malabsorption or increased losses. For example, in the Nutrition Crisp, the predicted prevalence of inadequate intakes of vitamins A, E, and B-12 and riboflavin was also very high (37). In Mexico, analysis of blood samples in a subsequent study of preschoolers of the same age and in the same communities confirmed the high prevalences of deficiencies of iron, zinc, vitamin A, riboflavin and vitamin E (L. Allen, unpublished observations, 1998) and of vitamin B-12 (38) that were predicted from dietary data in the Nutrition Crisp.

The cost of adding zinc to existing supplements is minimal compared with the costs of manufacture and distribution. An informal review of bulk suppliers revealed that the price of zinc (per milligram, as sulfate) ranges from one third to three times that of iron (per milligram, as ferrous sulfate), depending on the purity and hydration of the salt. In conclusion, if the decision is made to provide zinc supplements, serious consideration should be given to the simultaneous inclusion of other micronutrients.

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