

Low Risk of Adverse Effects from Zinc Supplementation

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About 2 million children die each year from diarrhea that is largely preventable. Recommendations for the clinical management of acute diarrhea were updated recently by WHO and UNICEF and now include the use of new lower concentration oral rehydration salts (ORS) and zinc supplementation for 10-14 days. USAID has requested MOST to support the rapid adoption of these new recommendations, and this brief is a component of that support. It reviews the available evidence on the safety of zinc supplementation in children, summarizes reports of adverse effects from both long-term and short-term studies, and concludes that zinc supplementation is a safe and effective treatment for diarrhea.

Zinc is an essential micronutrient that can be found in all tissues of the body and is essential for cell growth, differentiation, and DNA synthesis.¹ In addition, zinc is essential for the maintenance of a healthy immune system.² Human zinc deficiency was first identified in the 1960s in growth-retarded adolescent boys in Egypt by A.S. Prasad.³ Recent population level analyses from food balance sheets have estimated that 21% of the world's population is at risk for zinc deficiency.⁴ Children in many developing countries around the world typically consume fewer animal products than adults, which likely results in an underestimation of the prevalence of zinc deficiency among children, especially in the developing world. WHO has identified zinc deficiency as a major risk to child health, and they have linked it to morbidity from diarrhea (10%), lower respiratory tract infections (6%), and malaria (18%), accounting for 0.8 million child deaths per year.⁵

The International Zinc Consultative Group (IZiNCG) revised the recommended dietary allowances (RDAs) in 2004.⁶ These recommendations suggest the following:

Group	RDA of Zinc
Infants	4-5 mg
Toddlers between 1 and 3 years of age	3 mg
Children between 4 and 8 years of age	4-5 mg
Non-pregnant women	8-9 mg
Pregnant or lactating women	9-13 mg
Men	13-19 mg

These recommendations take into account differences in diet and are based on a standard reference body weight. Children receiving diets higher in phytate, which is found in unrefined cereals, will need to consume more zinc each day to achieve the physiologic requirement. In addition, these guidelines are for healthy children and do not take

into account the excess zinc losses during an episode of diarrhea,^{7,8} or the extra zinc required for catch-up growth and development.

In extensive safety studies undertaken in laboratory animals, zinc has been shown not to be carcinogenic, mutagenic, or teratogenic.⁹ In addition, the human body has efficient homeostatic mechanisms that regulate the absorption and retention of zinc, which decreases the likelihood of toxic build up in the body.¹⁰ Adult zinc toxicity can occur from moderately high intakes of zinc (> 150 mg/day — approximately 10 times the IZiNCG RDA) over a long period of time or from ingestion of > 1 g of zinc (more than 60 times the IZiNCG RDA) by overdose via supplementation or intravenous feeding.¹¹ Ingesting too much zinc at once can cause gastric distress and the typical signs and symptoms that are often associated with food poisoning.

High doses of zinc for long periods of time may lead to a lower concentration of plasma lipoproteins and decrease copper absorption.¹¹ Decreased copper status may also inhibit the transport of iron and result in anemia.¹² Although zinc-induced copper deficiency and the resulting anemia is serious, it occurs only after excessive zinc intake over a long period of time and is easily corrected by adjusting the intake levels of zinc and copper accordingly.¹⁰ Supplements of zinc and iron may also compete for absorption in the body.

There have been cases of acute, yet reversible adverse reactions reported from inhaling zinc vapors — a condition known as zinc fume fever — and from ingesting food or drink stored in galvanized containers.¹⁰ There are also a number of reported cases of adverse effects due to excessive zinc intake. The majority of these cases occurred



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in adults who knowingly ingested many times a normal daily dose of zinc over a long period of time. Even in the most extreme cases of more than 1 gram of zinc taken daily for many months, the majority of patients recovered from all signs and symptoms, including fatigue, gastrointestinal discomfort, and anemia as soon as zinc intake was decreased and serum zinc returned to within normal range.

In a WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, report, there were 50 cases of adverse effects of oral zinc sulfate including 56 clinical signs and symptoms. The majority of these were cases involved multiple drugs being given to or taken by the patient at the same time, so identifying the cause of the sign(s) and/or symptom(s) was not always possible. The cases documented in the report all varied in dosage, patient age, certainty of causality of association, and number of additional drugs. There were only two reported cases where the likelihood of causation by zinc was “certain”; 20 reported cases where the likelihood was “possible”; and nine where the likelihood was “probable.” The level of causation could not be established in the other reported cases. There were four reports of possible adverse responses to zinc ingestion among children less than 10 years of age.

Zinc and Diarrhea Treatment — Evidence from short-course supplementation trials

After more than 20 years of extensive research, zinc supplementation for the treatment of diarrhea is now recommended by WHO and UNICEF.¹³ Current recommendations are for 10–14 days of supplementation for all episodes of diarrhea among children under 5 years of age. Infants less than six months of age are to receive 10 mg daily and children 6 months–5 years of age are to receive 20 mg daily. These doses have been proven both effective and safe for treatment during diarrhea.

To date there have been no reports of severe adverse reactions from any form of zinc supplementation for the treatment of diarrhea. Trials have included more than 8,500 children who have participated in efficacy trials in both the placebo and zinc study arms and nearly 12,000 child-years of observation from one large effectiveness trial. The zinc doses have ranged from 5–45 mg per day and have been well-tolerated in diverse settings. Trials have found no differences in adverse reactions based on the different zinc salts used in supplementation trials, which are zinc sulfate, acetate, and gluconate.

Presently, the only reported side effect of zinc supplementation has been vomiting. Of the seven trials that have

reported on incidences of vomiting, only two reported more vomiting in the zinc supplemented vs. the placebo children.^{14,15} One trial reported higher vomiting than control when zinc was given with multiple micronutrients but not when given alone.¹⁶

Copper status has been evaluated in four trials. Three of the four trials did not find a difference in serum copper status after supplementation.^{14,17,18} One trial did find a significant trend of decreased copper status when comparing zinc supplemented children to non-zinc supplemented children.¹⁹ However, these children were malnourished with persistent diarrhea at baseline. Overall, there is no substantial evidence of short-term zinc supplementation for the treatment of diarrhea adversely affecting copper status.

In addition to trials treating diarrhea, there have been several trials assessing the efficacy of zinc for the treatment of pneumonia, malaria, measles, and the common cold. Treatments have typically included approximately 20 mg per day for the duration of the illness, which is typically less than two weeks. There have been no serious adverse events linked to zinc supplementation reported in these studies.

Long-term supplementation trials

There have been a number of long-term supplementation trials among young children and pregnant women. In children, these trials have supplemented children for improved growth and the prevention of pneumonia, diarrhea, and malaria. In 1999, a review of seven zinc supplementation studies for the prevention of diarrhea and pneumonia was published.²⁰ These trials were conducted in a variety of study populations with varying baseline nutritional status. Supplementation ranged from 5–20 mg Zn/day for up to one year. No adverse events were reported in these studies. There have been two studies supplementing children with zinc for the prevention of malaria. Children were supplemented with up to 70 mg Zn two times/week for up to 1.25 years, and no severe adverse events were reported.

In one supplementation trial of low birth weight infants zinc demonstrated not only the safety, but the benefits of daily supplementation among these vulnerable babies.²¹ Five mg of zinc was provided to 581 Indian infants age 30–284 days. Infants who received the zinc supplementation had a 32% decreased risk of death over the study period. There were five deaths among infants receiving zinc and 15 deaths among infants who did not receive zinc. There were no adverse events linked to zinc supplementation in this trial.

There have been several trials of zinc supplementation among pregnant women.²² Because the demands of zinc increase during pregnancy, zinc supplementation may provide benefits to the pregnant mother and the growing fetus, especially in countries where zinc intake is lower than the recommended standards. Although the benefits of maternal zinc supplementation have yet to be confirmed, there have not been any published reports of adverse events during these supplementation trials in either the pregnant women or their infants.

Precautions

As with any treatment, drug, or vitamin, zinc supplements should be kept in a safe place to prevent the accidental ingestion of more than the recommended dose. In the rare event that a child would consume multiple zinc supplements, it is likely that he/she would quickly vomit. There is no evidence suggesting further adverse events would occur, but as with any accidental ingestion of medication, the child should be taken to a healthcare provider. The risk of adverse events occurring from recommended supplementation schemes is extremely low, but the zinc supplement should be kept in a safe place to prevent unnecessary accidents.

Conclusion

Zinc supplementation is a safe and effective treatment for diarrhea. Zinc has also been shown to be safe in long-term supplementation studies. The most severe adverse events from supplementation trials have been vomiting in some cases and a slight decrease in copper status in some children. Neither of these has been shown to cause any long-term harm. Although there have been case reports in adults of excessive zinc intake, even the adverse events in these cases have been limited to short-term morbidity, and few have resulted in any long-term sequelae.

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