Discussion on Zinc in Maternal and Child Health

Zinc and Infection
There are ongoing studies in infants and young children of developing countries providing data to begin estimating prevalence of inadequate zinc intakes. Relatively good models now exist to examine the efficiency of absorption in various situations and the effect of phytate as the major factor affecting absorption. The issue was raised about the value of conducting more bioavailability studies, while the major contributing factor is the prevalence of diarrhea in the population (Dr. Allen). In response, the speaker (Dr. Hambidge) agreed with the point made, and indicated that the cornerstone of normal condition is required before expanded to cover infectious diseases. Eventually, both models are needed. Data have begun to emerge in relation to possible inflammation role in the gut, and further studies are required to elucidate whether part or whole of zinc deficiency problem is due to infection.

The issue of how acute infections including diarrhea and respiratory tract infections affect zinc requirements in children followed (Dr. Mobarak). Dr. Hambidge clarified that earlier works have shown that excessive zinc is lost in diarrheal fluid, so more zinc is needed to compensate for this loss. In addition, one may need additional zinc to correct for deficiency which is likely to be significant in this situation. The inquiry was then made of why given only zinc in diarrhea when other micronutrients could have been lost as well. The response was that while oral rehydration solution (ORS) is the core treatment, the benefit of zinc in diarrhea was clearly shown in earlier works by Bhutta et al. [1]. However, the same strength of evidence on other micronutrients and ORS for diarrhea treatment is lacking at the present time.

A question of whether zinc requirement in HIV population differs from normal population (Dr. Samburu) was addressed by Dr. Fawzi. So far, there are a few trials that investigated whether giving zinc supplements to HIV-infected individuals have a benefit. Earlier observational studies reported a sort of mixed
evidence, and some of the observational studies suggested that zinc was beneficial as low serum zinc was associated with harmful outcomes in terms of disease progression. Another observational study demonstrated that actually zinc intake was also harmful, so possibly reflecting a U-shaped relationship. These studies were all observational with certain limitations. As far as clinical trials are concerned, there are a few providing a sort of mixed evidence. In South Africa, zinc was beneficial in reducing diarrhea, while one study in Tanzania among pregnant women suggested no effect on CD4, CD8 or clinical outcomes. A third study more recently in the US among HIV drug users suggested that zinc supplements were actually beneficial in slowing disease progression particularly among individuals with advanced HIV. These were individuals with zinc deficiency, and the outcome was zinc supplements reduced the risk of failing on their antiretroviral therapy. So, the evidence is mixed and requires further studies (refer to the article by W. Fawzi in this book).

Zinc and Infant Growth

The issue concerns infants who are born growth retarded and whether zinc requirements differ between infants who are small for gestational age (SGA) and normal infants, and if there are any data available in terms of tracking of zinc from those pregnancies (Dr. Bhutta). Dr. Hambidge refers to the work of Dr. Nancy Krebs in this area with exchangeable zinc pools that shows lesser quantities of zinc in the zinc pools of SGA infants compared to those of controls. The follow-on comment (Dr. Solomons) pointed out that in animals with restricted growth, the nutrient requirements are reduced. Similarly, if the infant is primarily not growing and zinc in growing infants has to do with laying down of tissues, then zinc requirement will be reduced. On the other hand, when infant enters growth spurts, then requirements will go up because the amount of tissue being laid down is rapidly expanding.

Because zinc is one of those nutrients that dramatically falls in breast milk over a period of time, this phenomenon leads to the issue of zinc supplementation for both the growth-retarded and/or preterm babies, besides providing iron to prevent iron deficiency anemia (Dr. Mendoza). Dr. Hambidge indicated that it’s quite extraordinary in the term infant situation how rapidly the physiologic decline in milk zinc takes place, and levels are very low by 6 months in the term infant; similar situation could occur in the preterm infant with a lot of other issues and challenges happening at the same time.

The next discussion took the direction of iron and zinc absorption. The concern is that in preterm nutrition, the suggestion has been made to start giving iron quite early. Therefore, if iron affects zinc absorption, then zinc requirement should be increased in these preterm infants (Dr. Garg). Dr. Hambidge agreed that zinc should be given too.

A comment was also made that studies in infants and adults showed that when iron is given together with zinc in foods, there is no effect on zinc absorption.
**Bioavailability**

A question was raised concerning bioavailability of different zinc compounds, citing animal studies done in Beijing that reported zinc gluconate as the most bioavailable, followed by zinc sulfate and zinc lactate, respectively (Dr. Ludan). In response, Dr. Hambidge indicated that all water-soluble compounds are bioavailable. With respect to iron, calcium and phytate, the old data suggested that calcium phytate reduced zinc bioavailability. However, current modeling where iron and calcium data are available showed that absorption of zinc is increased, not decreased. Based on the assumption that the zinc and the iron were taking up some of the binding sites on the phytate, it increased the R² value from 0.81 to 0.87. Therefore, this issue needs to be revisited.

**Stable Isotope Technique**

The issue on the use of the stable isotope technique to measure zinc status and the usefulness of this technique to determine the exchangeable zinc pools was raised (Dr. Hurrell). The response is that there is no answer on this matter yet. However, at the time being, with the absorption figures as shown in the presentation as well as good dietary data that include zinc and phytate values and random sub-samples of serum zinc from diverse studies, these should result in useful estimates of population zinc status.

**IOM and IZiNCG Estimates**

Reconciliation of IOM [2] and IZiNCG [3] estimates is recommended. IZiNCG is planning a review on zinc requirement estimates to take into consideration new data from studies published after 2001. The model as presented on the inhibitory effects of phytate on zinc absorption should be taken into consideration (Dr. Wasantwisut).

Overall, the paper is well presented and raised valid points for consideration with regard to zinc requirements, including the role of infection, preterm infant growth, interaction of iron and zinc, bioavailability of zinc in relation to iron, calcium and phytate, as well as the usefulness of stable isotope technique and modeling for estimation of population zinc status.

**Discussion on ‘The Role of Zinc in Child Health and Survival’ by R.E. Black and C.F. Walker**

**Zinc and Diarrhea**

A question was raised regarding the reason why zinc given with ORS for the treatment of diarrhea is more effective in developing countries compared to developed countries (as demonstrated in ESPGAN study in Europe). Infants who are exclusively breastfed in the first 6 months are unlikely to be zinc deficient (Dr. Haschke). The response (Dr. Black) is that little information exists
on zinc in treatment of diarrhea in high-income countries; there is a potential deficiency in the infant age group. In the first 6 months, this may not be the issue, but the 6–11 months is certainly more equivocal, and zinc deficiency is likely to occur. A comment followed that Bangladeshi children have subclinical zinc deficiency due to low zinc in soil and foods being produced. Zinc therapy for diarrhea is recommended; the question is whether 20 mg of zinc in young children is too high and whether it could have an adverse effect (Dr. Alam). Dr. Black clarified that often a lower dose (10 mg) is used in very young children. In fact, where 20 mg has been used for a short time period, there are virtually no side effects. In the meta-analysis of all of the trials, there is a few percent additional vomiting in the zinc versus placebo groups, but there is no interference with oral rehydration therapy or clinical outcome. Similarly, an inquiry was made on possible side effects in certain studies which gave as much as 45 mg dose to the under-five children (Dr. Kalantari). In response, the 45-mg dose was used in a couple of therapeutic trials, not in a daily preventive dose, and resulted in more side effects. Such high dose apparently did not lead to any more benefit than using a lower dose in the therapy of diarrhea. The WHO recommendation is 20 mg except for younger children where the dose is lower [4].

With respect to the mechanism of diarrhea for the 20-mg zinc dose (Dr. Hurrell), this may be due to potential immune mediation, probable physiologic or pharmacologic reasons and anti-secretory effects observed in animal models. Since many of the causes of diarrhea have very different pathogenesis with respect to mucosa and secretory factors and so forth, an inquiry was made whether zinc effect is more likely to be observed with certain kinds of diarrhea such as bacterial versus viral (Dr. Rosenberg). The response is that most trials did not conduct ideological investigation. There are two trials reporting benefits of zinc in *Shigella* and cholera. It’s quite important in syndromes like cholera or ideologic specific diarrhea like *Shigella* to show zinc does work because those are the ones that would stand out. From a public health standpoint, the overall effect such as that of ORS matters eventually, and implementation should not be held back because of lack of ideological reasons.

For the benefits in diarrhea, this appears to be specific to zinc per se (Dr. Manalaysay), while the probable usefulness of other micronutrients (Dr. Mobarak) would require supportive evidence. Additional comment was made (Dr. Bhattacharya) that in clinical practice, pediatric patients with bacterial infection and bloody diarrhea received i.v. fluid, antibiotics and zinc supplements upon discharge. The follow-up results were excellent with the trend of improved appetite and faster weight gain.

Another inquiry was whether the existing knowledge on formulations of zinc for the treatment of diarrhea is sufficient to indicate that the type of preparation does not matter. In addition, there has been some suggestion that maybe the effect seen in diarrhea is pharmacologically dependent upon the dosage, and if the same amount is divided into 3 doses over a 24-hour period, one doesn’t see
the same effect (Dr. Bhutta). The response is that there are no data to respond to these issues, and further studies are required.

The consistent lack of zinc effect in the <12 months age group has been raised (Dr. Wasantwisut), and the reason could be the increased demand due to rapid growth spurt as well as the immune system which cannot be met through the zinc dose given. In addition, a good biomarker of zinc status is needed besides serum zinc, which increases during the period of supplementation. In a developing country, recommendation on zinc prevention or treatment (Dr. Hadad) should be based on dietary data or population level of serum zinc measurement.

Other Benefits of Zinc
An issue was raised with respect to routine provision of zinc to children beyond treatment of diarrhea (Dr. Fawzi). On the one hand there is clear benefit on prevention of diarrhea, on the other hand when zinc is given with iron there is some negative interaction. In the context of Sprinkles, the question is whether there is a certain ratio that should be avoided or promoted. In response, there is good evidence that zinc supplements have a benefit on infectious disease outcomes, and that the benefit on growth may be small. Some equivocal evidence exists of interference or reduction of that effect if zinc is given with iron. It’s not yet known concerning the right balance of zinc versus iron in a supplement or a Sprinkle micronutrient powder. The suggestion to go for equal molar ratios lacks supportive evidence on functional outcomes or increases in serum zinc. The supplementation trials that gave zinc only, almost always demonstrated an increase in serum zinc. In this context, a comment was made (Dr. Bhutta) that so far, the three large Sprinkle studies have not been able to show any impact on zinc, using either a 7.5- or a 10-mg dosage.

Besides the treatment of diarrhea, an inquiry was made whether zinc may benefit pneumonia or urinary tract infection and other inflammatory disorders (Dr. Manalaysay). The response is that solid evidence in human trials is required prior to issuing any recommendation. The potential role of zinc in treating asthmatic symptoms with respect to pneumonia has been mentioned (Dr. Bhattacharya), and deserves further attention.

Supplements versus Foods
The people who have got sustained zinc supplementation as prevention for infectious morbidities would in fact over time meet and exceed the requirements. On the other hand, a question was raised whether the preventive aspect of the supplemental exposure would withhold if people were fortified or their diet diversified to meet their nutrient requirements within the range of recommendations (Dr. Solomons). In response, in zinc-replete populations, there would be no therapeutic benefit. With supplements, one could possibly achieve normal zinc status during the period of supplementation and a couple of months afterwards. In the case of fortification, the same scale of achievement has not
been shown. The lack of evidence on improved zinc status from fortified foods or Sprinkles versus supplements could be due to the fact that the absorption of zinc in supplements is much higher than from foods, so a higher fortified dose may be required to reach similar outcomes (Dr. Hurrell). Another factor could be that there are no sensitive methodologies or biomarkers to measure the impact of zinc in foods. More studies are on the way to unravel the issue surrounding the formulation and whether or not adding Sprinkles or adding zinc to Sprinkles per se or zinc to Sprinkles without iron is a means of assessing their bioavailability (Dr. Bhutta).

An inquiry was made regarding multiple interventions, in this case zinc in Sprinkles and zinc supplements for diarrhea, of whether there is a risk of toxicity (Dr. Penny). The response was that there has to be evidence on the impact of zinc in Sprinkles on improving zinc status before judging potential excess level of intake. In addition, the safety margin with zinc is incredibly high. Additional comment was made that the efficacy of supplements is different from Sprinkles or micronutrient powder in food due to phytic acid. A study has just been completed where micronutrient powder that contains endogenous phytase actually reduces the phytic acid content of the complementary food resulting in a significant increase in serum zinc (Dr. Zimmermann). In addition, a randomized control trial using different dosages of zinc against the background of Sprinkles is underway and should provide the results by the end of the year (Dr. Bhutta).

Overall, the paper was well presented and generated a lot of discussion, primarily on the benefits of zinc in diarrhea and other infectious diseases and the mechanism involved, the ideological spectrum of pathogen-specific environment, the differences in efficacy trials of zinc supplements compared to food-based strategies, and the concern of excess level of intake with multiple interventions.

Emorn Wasantwisut

References


