

Dose-Response Trial to Assess the Efficacy and Risk of Zinc Supplementation, With or Without Copper, on Plasma Zinc Concentrations, Morbidity, Markers of Copper Status and Growth of Young Ecuadorian Children at Risk of Zinc Deficiency

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INTRODUCTION

The optimal dose and safe upper limit of Zn supplementation for young children are not known. Adverse effects of excessive Zn intake include a decrease in Cu status and alterations in lipoprotein concentrations. Therefore, the objective of this study was to compare the effects of different doses of Zn supplements, with or without Cu, on indicators of Zn and Cu status and other functional outcomes in young children at risk of Zn deficiency.

METHODS

The study was a randomized, double-masked, placebo-controlled, community-based, dose-response trial carried out in Ecuadorian children 12 to 30 months of age with initial length-for-age z-score (LAZ) < -1.3 with respect to World Health Organization (WHO) reference data and absence of severe anemia. All children received 1-3 months of supplemental Fe prior to entering the study, as per Ecuadorian Ministry of Health policy.

Interventions

Participants received one of five liquid supplements containing 3, 7, or 10 mg Zn as sulfate, 10 mg Zn + 0.5 mg Cu as sulfate or placebo. Supplement consumption was supervised 3-5 times per week during which time morbidity data were also collected from children's care-givers using a systematic, symptom-based questionnaire and pre-defined illness categories.

Outcome Measures

Anthropometry and biochemical indicators were assessed in all groups at 0, 3 and 6 months of intervention. Weight and length measures were converted to nutritional status indices of weight-for-age z-score (WAZ), weight-for-length z-score (WLZ) and LAZ in relation to WHO child growth standards (WHO Anthro 2005).

Biochemical markers included plasma or serum concentrations of Zn, Cu, ceruloplasmin activity, ferritin, C-reactive protein, HDL and total cholesterol and whole blood concentrations of hemoglobin. Additionally, erythrocyte Zn-Cu superoxide dismutase (ESOD) activity was analysed in relation to erythrocyte hemoglobin concentrations.

RESULTS

There were no significant differences in children's mean age, anthropometrics or plasma Zn concentrations by treatment group at baseline (see Table), and there were no significant group-wise differences in the change in serum concentrations of ferritin or CRP or in the change in whole blood concentrations of hemoglobin.

Beneficial effects of Zn intervention

The change in plasma Zn concentration from baseline was directly related to the Zn dose, and there was a significant group-wise difference in the change in plasma Zn concentration ($p < 0.01$). There was a significant difference between groups in the incidence of diarrhea ($p = 0.01$), and the effect of treatment group on incidence of diarrhea was significant at 3 and 7 mg Zn/day, but not at 10 mg Zn/day (see Table 1). There were no other significant group-wise differences in reported morbidity, and there was no significant difference between groups in change in anthropometry.

Possible adverse effects of Zn intervention on markers of Cu status

There were no significant differences between groups in change in plasma or serum concentrations of Cu, ceruloplasmin activity, HDL or total cholesterol. Nor were there differences among groups in change in ESOD activity.

Table 1 . Baseline characteristics and changes in selected outcomes by intervention group.

Intervention by initial characteristic or outcome (group-wise p-values)	Intervention group				
	Placebo* n=116	3mg Zn* n=113	7mg Zn* n=117	10mg Zn* n=116	10mg Zn + 0.5mg Cu* n=117
Initial age, mo ($p=0.90$)	21.2 ± 5.3	20.9 ± 5.1	20.8 ± 5.2	20.6 ± 5.6	21.2 ± 5.5
Initial LAZ ($p=0.74$)	-2.26 ± 0.73	-2.26 ± 0.60	-2.32 ± 0.71	-2.21 ± 0.57	-2.26 ± 0.60
Initial plasma Zn conc, ug/dL ($p=0.34$)	71.6 ± 16.2	71.7 ± 14.6	71.8 ± 13.5	72.4 ± 14.7	75.3 ± 15.3
Change in plasma Zn conc, ug/dL ($p < 0.01$)	-1.0 ^a ± 12.6*	14.2 ^{ab} ± 30.5	19.8 ^b ± 36.7	22.1 ^b ± 29.1	15.5 ^b ± 23.8
Diarrhea incidence, #/100d ($p=0.01$)	1.90 ^a ± 2.11	1.29 ^b ± 1.72	1.18 ^b ± 1.58	1.57 ^{ab} ± 1.63	1.37 ^{ab} ± 1.47
Change in LAZ ($p=0.48$)	0.11 ± 0.32	0.11 ± 0.30	0.15 ± 0.29	0.05 ± 0.33	0.10 ± 0.30

*mean ± SD; different letters indicate significant differences as analysed by ANCOVA

CONCLUSIONS

Final plasma Zn concentrations reflected the level of daily Zn supplementation, indicating successful administration of the supplements. Provision of as little as 3 mg Zn/day reduced the incidence of diarrhea, and there was a reduction in mean incidence of diarrhea in children receiving 10 mg Zn/day although this reduction was not statistically significant. These findings indicate that further dose-response research may be needed to determine whether the optimal dose of prophylactic supplemental Zn is below 10 mg/day for this age group.

Our findings, that provision of 10 mg supplemental Zn did not adversely affect biochemical indicators of Cu status or lipoprotein concentrations, provide evidence that the recommended upper limit for Zn in young children may need to be reassessed.

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REFERENCES

World Health Organization (WHO) (2005) *Anthro 2005*. Downloaded July 2006 from: <<http://www.who.int/childgrowth/software/en/>>. Version for SAS, May 24, 2006