The effect of zinc supplements on plasma zinc and copper levels and the reported symptoms in healthy volunteers

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ABSTRACT Information from animal studies has demonstrated the harmful effects of zinc supplementation on copper transport. Although some studies have been carried out in humans, the effect on humans has not been as well documented as the effect on animals. Forty-seven healthy volunteers (26 women and 21 men) took part in a double-blind cross-over trial which lasted for 12 weeks. The subjects were asked to take 50 mg of elemental zinc (as 220 mg zinc sulphate) or placebo, three times a day for six weeks. Venous blood was collected for the analysis of plasma levels of copper and zinc. Symptoms, which included headaches, abdominal cramps, nausea, loss of appetite and vomiting, were registered from 84% of women and 18% of men. Six female volunteers discontinued the trial; five owing to gastric irritation and one owing to consistent headaches. Plasma zinc levels rose significantly in both men and women, the increase being 36% and 57%, respectively. Plasma copper levels did not change significantly. Our study suggests that the gastric discomfort that is associated with zinc supplementation may be related to body weight as symptoms were reported from the lower-weight volunteers. Our study also shows no detrimental effect of 150 mg of zinc a day on plasma copper levels in healthy volunteers over a period of six weeks. (Med J Aust 1987; 146: 246-249)

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Zinc has been used as a therapeutic agent since the 1960s and has proved to be effective in several circumstances.[1] Supplements of approximately 150 mg of zinc a day in the form of zinc sulphate have accelerated the rate of healing of ulcers,[2-4] bedsores[5] and surgical wounds.[6] However, long-term supplementation with 150 mg of zinc a day has resulted in reduced plasma copper levels in adult patients who suffered from sickle-cell anaemia[7] and coeliac disease.[8] Short-term supplementation (five weeks) with 50 mg of zinc a day did not affect plasma copper concentrations although the activity of erythrocyte superoxide dismutase, an indicator of copper status, was reduced.[9] Small increases in zinc intake after the depletion of zinc stores through dietary restriction reduced copper retention and resulted in reduced plasma copper levels.[10] Metabolic studies have shown antagonism between increases in dietary zinc intake and copper uptake,[11] and, from studies in rats*, this is believed to be due to the competition for binding sites in the intestinal mucosal cells.[12] Thus, the dietary antagonism between copper and zinc can be reflected in plasma levels of copper.

Although supplements of a large magnitude are administered by prescription under special circumstances, similar high doses can be obtained as over-the-counter preparations from "health-food" outlets and pharmacies. The ingestion of zinc is encouraged for indications such as an improved sex life and the prevention of hair loss and colds.

As part of a study of the effect of zinc on plasma cholesterol levels,[13-14] 47 healthy volunteers received a supplement of 150 mg of zinc a day over a period of 12 weeks. The symptoms that were observed over the study period appear worthy of detailed discussion and are reported in this paper. The effects of zinc supplements on the concentrations of copper and zinc in the plasma are also reported.

Subjects and methods

After the receipt of informed consent, 26 women and 21 men, most of whom were students or staff members of The University of Sydney, were

recruited as volunteers in a double-blind cross-over trial that lasted for 12 weeks.

As part of the screening process, potential volunteers who were taking oral contraceptive agents or any medication were excluded from the study. Subjects were asked not to alter their eating and exercise patterns for the duration of the study. In addition, blood was collected in the non-fasting, state and a biochemical profile (multiple biochemical analysis, MBA-20) was determined on the serum. All volunteers exhibited normal profiles except for one man who had an elevated plasma cholesterol level.

Zinc was administered as capsules that contained 220 mg of zinc sulphate and provided 50 mg of zinc (Zincaps, Protea Pharmaceuticals). The subjects were instructed to take a capsule three times each day with meals. Identical capsules that contained lactose were used as the placebo. Volunteers were allocated at random to zinc treatment for six weeks that was followed by a placebo regimen for six weeks, or vice versa.

The volunteers were seen at three-weekly intervals for the issue of capsules and were contacted weekly in order to reinforce their compliance with the trial. Measurements of height and weight were also carried out. Any signs or symptoms were recorded in response to a general enquiry about problems that they might have experienced with the study. However, as the volunteers were seen regularly, symptoms were not prompted by a checklist or questionnaire as this could have encouraged or evoked preconceived symptoms.

Plasma copper and zinc levels were measured by atomic absorption spectrophotometry (Varian, AA-575). Blood was collected into plastic syringes and transferred to polycarbonate tubes that contained hepafin. Plasma was separated and frozen for subsequent analysis. Plasma was deproteinized and copper and zinc levels in the supernatant were measured with the appropriate standards.[15]

Results

Symptoms were registered from 84% of 26 women and 18% of 21 men; they included headaches, abdominal cramps, nausea, loss of appetite and vomiting.

Symptoms	*Men (n)*	*Women (n)*
Abdominal cramps	1*	6
Vomiting	2	6
Nausea	1	4
"Bloated" feeling	0	4†
Loss of appetite	0	2
Metallic taste in mouth	0	4†
Headaches	1*	1

*Symptom reported while receiving placebo.
†Symptom reported from one volunteer during the placebo period.

Although a sex difference cannot be ruled out, it is likely that the high number of complaints from female, as compared with male, volunteers is related to the difference in body weight (Table 1) and thus a *25%* higher dose/kg ratio in women (0.84 ±0.11 mg/kg versus 0.68 ±0.10 mg/kg; single dose divided by body weight ± SD). This is more evident when the number of complaints is matched with the dose/kg ratio (Table 2) as the number of complaints increases with subjects of lower body weight. Three volunteers reported symptoms during the, placebo period and two volunteers reported"

TABLE 1: Age and anthropometric description of the study population

Sex	Age (years)	Body weight (kg)	Body mass index (kg/m²)
Women	26.8±7.1	61.3±8.8	22.0±2.8
Men	28.2±9.2	73.9±9.2	23.4±2.7

TABLE 2: Effect of the zinc dose (mg)/kg body weight ratio on the number of complaints* by male and female volunteers

Group	Dose (mg)/kg ratio	Number of volunteers	Number of complaints	
1	0	21 men	1	6.7%
		24 women	2	
2	≥0.4<0.6	3 men	0	
3	≥0.6<0.8	17 men	2	25.9%
		10 women†	5	
4	≥0.8<1.0	2 men	1	66.7%
		11 women†	9	
5	≥1.0<1.2	2 women	2	100%

*Significantly different by means of the χ^2 test ($P<0.001$).
†Of the six women who discontinued the trial, two came from Group 3 and four from Group 4.

TABLE 3: Plasma copper and zinc concentrations* after supplementation of diet with zinc

Sex	(n)	Before zinc supplementation	After zinc supplementation
Plasma zinc levels			
Men	21	15.1±2.5	20.6±4.6†
Women	20	14.8±2.5	23.2±6.3†
Plasma copper levels			
Men	21	12.0±1.9	11.7±2.0
Women	20	14.0±3.0	13.4±3.0

*Values expressed as μmol/L, mean ± SD.
†Significantly different from initial values by the paired Student's *t*-test ($P<0.001$).

symptoms when they ingested two zinc capsules simultaneously.

All together, six volunteers discontinued the study: five of whom did so because of abdominal symptoms and one because of persistent headaches. All were women with a dose/kg ratio of 0.86 ±0.12 mg/kg.

Plasma zinc levels rose significantly in both men and women after six weeks of zinc supplementation (Table 3). The rise in women was slightly greater than that in men, in spite of similar baseline values. Very small decreases in plasma copper levels (Table 2) were also seen. However, these differences did not reach statistical significance.

Discussion

Abdominal discomfort has been ascribed to zinc supplements in previous studies,[16] although the dose/body weight ratio has not been implicated. All volunteers in this study were instructed to take one capsule with each meal; however, complaints were associated consistently with small meals (for example, with breakfast or morning tea) or no food when the capsule was taken.

Three volunteers reported abdominal symptoms during the administration of the placebo. However, they worked with other volunteers who received zinc treatment at the time and who withdrew subsequently from the study due to continued discomfort. Conversely, no symptoms were reported from two volunteers who received zinc treatment but who worked with two volunteers who received the placebo.

°Three female volunteers reported that they had sought medical advice after severe cramps and vomiting. These volunteers reported that they had informed the physician of their participation in the study. However, in all cases the physician reportedly dismissed zinc as the cause of the gastric irritation and diagnosed it as due to a "24-hour virus".

One volunteer discontinued the trial due to persistent headaches. Although headaches have been reported after exposure to zinc fumes,[17] the effect in our study is confounded by the presence of tartrazine in the capsules. Sensitivity to tartrazine may result in headaches in susceptible individuals.[18]

As expected, supplements of 150 mg of zinc a day for six weeks resulted in significant rises in plasma zinc concentrations in both men and women, the increase being 36% and *51%,* respectively. This difference also reflects the differences in body weights; female volunteers with lower body weights showed a greater increase in plasma zinc levels when compared with male volunteers when they received equal supplements of zinc.

The effect on plasma copper levels was less pronounced. The decreases in plasma copper levels that were seen in men and women were small (2°/o and 5%, respectively) and individual variation prevented them from being significantly different from the initial values. Thus, in a free-living healthy population that maintained its normal diet, no detrimental effect of zinc supplements on plasma copper concentrations could be seen. This is a similar effect to that which was seen with smaller supplements (50 mg of zinc a day) in men,[9] but different from the effect on plasma copper levels that was seen by Festa et al.[10] However, that study was a repletion study and not a supplementation one, which may explain the differences that were obtained. Furthermore, the reduction in plasma copper levels as seen in patients who received a supplement of 150 mg of zinc a day[7 8] was not seen here, possibly due to the duration of the supplementation period; the period in those studies was 12 months as compared with the six-week period in our study.

The association between body weight and symptoms may explain the high number of complaints from women as compared with men; the women in this study weighed significantly less than did the men. This difference in weight would be highlighted further if expressed as lean body mass as women have more fat as a percentage of body weight and thus a lower lean body mass than do men.[19] However, lean body mass could not be calculated from our data as skinfold thicknesses'were not measured.

Thus, the gastric discomfort that is associated with zinc supplements may be alleviated by maintaining a dose/body weight ratio of less than 0.8 mg/kg (Table 1) or by ensuring that the supplement is taken with a main meal. Our study also shows no detrimental effect of 150 mg of supplementary zinc each day on plasma copper levels in healthy volunteers over a pertod of six weeks.

Acknowledgements

We gratefully acknowledge the cooperation of the 47 persons who took part in this study. We would like to thank Ms Jane Allen for organizational skills; Ms Marija Gavranic for expert technical assistance; Dr Michael Turner (Protea Pharmaceuticals) for supplying zinc capsules; Dr David R. Sullivan (Royal Prince Alfred Hospital) who allowed the biochemical profiles to be carried out in his department; and Professor Stewart Truswell for his helpful advice. Samir Samman is the recipient of a University of Sydney Nutrition Research Foundation Scholarship.

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(Received August 75; *accepted December 10,* 7986)