

Oral Zinc in Normal Subjects: Effect On Serum Copper, Iron, Calcium and Histidine Levels

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Nutritional zinc supplementation has been increasing due to the recognition that zinc deficiency may play a role in a number of disorders and that the American diet is often lacking in zinc. Beneficial effects of zinc supplementation have been found in wound healing (Pories et al., 1967), hypogeusia (Schechter et al., 1972), hypogonadism and dwarfism (Prasad et al., 1963), complications of sickle cell disease (Brewer et al., 1977), acrodermatitis enteropathica (Neldner and Hambidge, 1975), and some forms of mental illness (Pfeiffer and Cott, 1974). Excess copper may be a factor in one type of schizophrenia which is characterized by low blood histamine levels. The low histamine level may be due to high levels of histaminase, a copper containing enzyme. High copper or iron levels and/or zinc deficiency may be factors in this condition which responds to zinc supplementation probably due to the antagonism between these ions.

In moderate amounts zinc is relatively non-toxic and produces few side effects, the main side effect being intestinal irritation which appears to be more prevalent with the sulfate form. Chronic ingestion of large amounts of zinc may produce copper and iron depletion with a resulting anemia which responds to treatment with copper and iron supplements.

We (Pfeiffer and Jenney, 1978 and Pfeiffer et al., 1980) have observed a patient who had low serum copper and little if any ceruloplasmin due to the ingestion of large amounts of zinc over a period of several months. Prasad et al., (1978) have also reported on a case in which hypocupremia and hypoceruloplasminemia were induced by zinc therapy involving 150 mg elemental zinc per day.

The present study documents the effect of a single ingestion of a zinc supplement on a variety of biochemical parameters over a four hour period. The long term administration of zinc results in the control of serum zinc levels by a number of homeostatic mechanisms. A study of the acute effect of zinc on a number of biochemical parameters might give some clues as to what mechanisms might be involved in its homeostatic control.

Methods

Fifty-five mgs of elemental zinc as the acetate, dissolved in 200 ml of water was ingested by four male and four female volunteer subjects who were laboratory personnel and had given their informed consent. Blood samples were drawn, before, ½ hour, 1 hour, 2 hours, 3 hours and 4 hours after ingestion. In addition to an autoanalyzer chem screen profile for 25 clinical chemistries, serum tryptophan and histidine levels were determined. Blood histamine, spermine, spermidine, lead, man-

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ganese, and aluminum levels were also determined as well as a complete blood count which was carried out on each sample.

All subjects had a placebo run in which they ingested 200 ml water. Subjects fasted prior to and during experimental runs. Zinc was administered in the form of the acetate to avoid any biological effects of the anion. Ingestion of 55 mgs zinc with the extreme range of body weight of the subjects provided extremes in dose range of 0.6 -1.5 mg/kgzinc.

Results

Serum zinc levels roughly doubled and reached a maximum 2 to 3 hours after oral administration. A good correlation was found between the maximum serum zinc level attained and zinc dose when dosage is calculated on the basis of body weight. $r = 0.960$ $t = 8.41$ (Figure 1). The higher serum zinc levels attained in female subjects as compared to male subjects (Figure 2) are due to differences in body weight. The ratio of maximum serum zinc level to zinc dose expressed in mg/Kg body weight is not significantly different in male and female subjects. The mean ratio of serum zinc to zinc dose was 340.6 ± 24.1 for females and 335.3 ± 16.8 for males. This difference was not statistically significant. Upon oral administration of the single oral dose, the serum zinc level rises rapidly reaching a maximum 2 to 3 hours after ingestion and then returns to base line at about 6 hours.

Table 1 presents mean trace metal levels pre-dose and after 4 hours for the zinc and placebo runs. No significant differences in

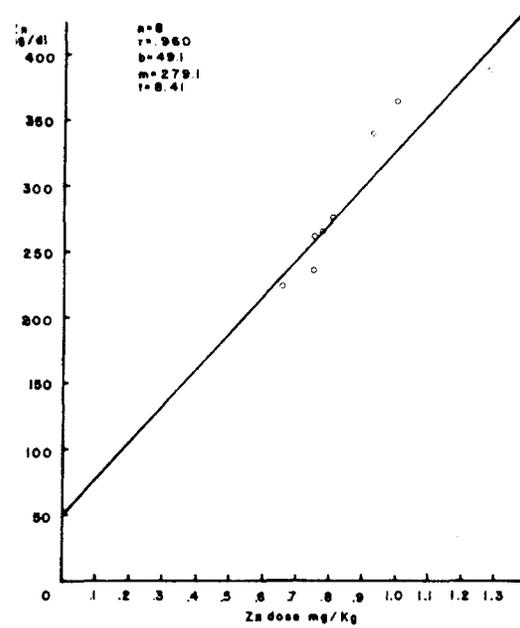


FIGURE 1
Correlation between zinc dose administered and maximum serum zinc level attained.

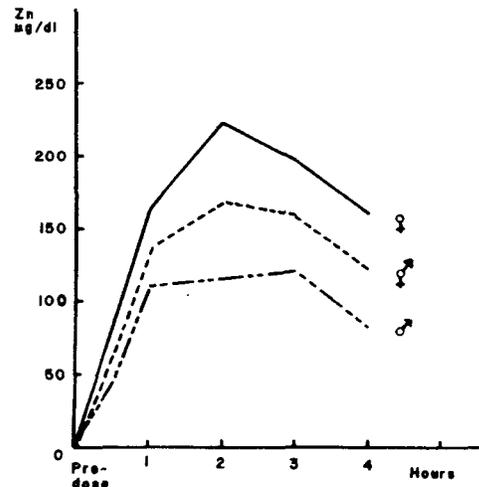


FIGURE 2
Increase in serum zinc over placebo levels in males and females upon oral administration of 55 mgs of elemental zinc.

	Zn run		Placebo run	
	PREDOSE $\bar{x} \pm s$	4 HOURS $\bar{x} \pm s$	PREDOSE $\bar{x} \pm s$	4 HOURS $\bar{x} \pm s$
Serum Zn ($\mu\text{g/dl}$)	118 \pm 17	237 \pm 66	117 \pm 19	117 \pm 16
Serum Fe ($\mu\text{g/dl}$)	104 \pm 30	85 \pm 29	97 \pm 40	100 \pm 44
Serum Cu ($\mu\text{g/dl}$)	117 \pm 28	117 \pm 28	114 \pm 24	110 \pm 21
Blood Pb ($\mu\text{g/dl}$)	1.2 \pm 0.4	1.1 \pm 0.4	1.1 \pm 0.4	1.2 \pm 0.4

zinc (Zn), iron (Fe) and copper (Cu) were found in the placebo run. In addition to the significant rise in zinc level in the zinc run there was a significant decrease in the iron level from 105 to 85 u/dl while no significant change was found in the copper level. The decrease in iron level of about 15 percent over the four hour period is real since it was found by two independent methods of iron determination. Iron levels were determined by a colorimetric procedure determined as part of the chem screen and by atomic absorption spectroscopy. Similar results were obtained by both methods. Evidence was obtained that this depression of the iron level after zinc ingestion may exist for as long as a week. Serum iron was measured 24 hours and 1 week after the zinc dose (Figure 3).

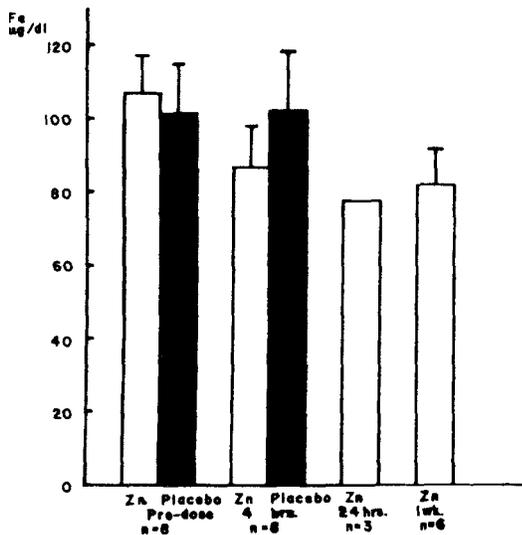


FIGURE 3
Effect of zinc administration on serum iron levels.

The cause of observed depression in iron levels is obscure although chronic ingestion of large amounts of zinc is known to interfere with the absorption of iron apparently through competition for protein binding sites in the intestinal mucosa. However, it is doubtful that this is the explanation for the rapid decrease observed in this study. It is more likely that a migration of iron from serum to tissue is responsible. In contrast to the effect on serum iron

levels, no change was found in serum copper levels over the four hour period, copper levels for zinc and placebo runs being unchanged. Copper depletion by large doses of zinc has been observed both in animals and humans upon chronic administration. To observe toxic manifestations of zinc one must ingest large amounts of zinc of the order of a gram or more per day. We and Prasad's group have observed copper depletion under these conditions.

The intake of large amounts of zinc is known to lower serum copper levels in both man and animals and produce in them signs of copper deficiency (Magee and Matrone, 1960; Sanstead, 1978). That a single acute dose of zinc did not have an effect on the serum copper level is not surprising. It may well be that this is a chronic effect which is not evident in this acute study. It has been postulated that the mechanism involved may be the induction by zinc of metallo-thionein synthesis which would regulate the amounts of copper and zinc absorbed from intestinal cells (Czerwinsky et al., 1974). The induction of regulatory mechanisms by zinc is highly probable because chronic administration of moderately high zinc dosages results in an initial increase in serum or plasma zinc levels which upon continued administration tend to reach a plateau level.

Chronic administration of moderate zinc levels in conjunction with vitamin supplements has been found to be useful in reducing the copper burden of many patients with psychiatric problems.

With chronic administration of moderate doses, homeostatic mechanisms come into play so that the serum zinc levels are not markedly elevated while iron levels are not markedly depressed. In the case of copper the effect is variable in that in subjects with high serum copper levels the level may be depressed, while in patients who may have a high tissue copper level there may be a rise in their serum copper levels until their levels do not necessarily reflect tissue levels of copper. It would appear that different mechanisms are involved in the interactions of zinc and iron and zinc and copper.

Significant decreases were found in

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	ZINC MEAN ± S.D.		PLACEBO MEAN ± S.D.	
	PREDOSE	4 HOURS	PREDOSE	4 HOURS
Histidine	1.54 ± .27 (p < .05)	1.21 ± .22	1.40 ± .24 (N.S.)	1.46 ± .25
Calcium	9.63 ± .45 (P<.05)	9.32 ± .59	9.85 ± .45 (N.S.)	9.49 ± .45

histidine and calcium levels during the zinc run in contrast to the placebo run. Over the four hour experimental period the mean histidine level dropped from 1.54 to 1.21 mg/dl while calcium dropped from 9.63 to 9.32 mg/dl (Table 2). These effects were significant at the .05 level when a paired t test was carried out on the data.

The metabolism of histidine and zinc appear to be closely linked. Simkin (1977) has shown in a chronic study in which zinc was administered over a 12 week period that as serum zinc levels rose the histidine level fell from 1.57 - 1.36xjg/dl. Histidine is known to effect zinc absorption but it is also felt that zinc and histidine form a complex which is readily excreted and may facilitate the excretion of zinc. This might be a reasonable explanation for the rapid change in histidine levels observed in this experiment.

Zinc is known to interact with calcium particularly with regard to cell membrane permeability. Several studies have shown an interaction between zinc and calcium in animals (Thompson et al., 1959, Hsu et al., 1973)

Calcium is known to form a complex with zinc and phytate which is more insoluble than zinc phytate (Oberleas et al., 1966) which may play a role in preventing zinc absorption.

No significant effects were found due to zinc administration on the other common biochemical parameters examined (Table 3) among which were total protein, albumin, globulin, serum enzymes, serum lipid, cholesterol, bilirubin, BUN, glucose, histamine, spermine, spermidine, immunoglobulin levels. Blood parameters did not show any significant difference in blood counts, hematocrit, hemoglobin or differential.

In conclusion, we find that ingestion of 55 mgs of elemental zinc in the form of acetate produces significant changes in a few biochemical parameters which are known to interact with zinc. Significant changes were found in serum histidine, iron and calcium levels. Alteration of those parameters in an acute experiment may indicate that the interaction of these factors may be involved in homeostatic mechanisms which regulate the level of serum zinc.

TABLE 3
Biochemical parameters showing no significant changes from placebo run upon administration of oral zinc

<p>SERUM glucose uric acid creatinine phosphorus BUN sodium potassium chloride tryptophan total lipid total bilirubin direct bilirubin total protein albumin globulin IgA IgM IgG</p>	<p>BLOOD lead manganese aluminum histamine spermine</p>	<p>HEMATOLOGY hemoglobin RBC WBC Hct MCHc MCH McV differential</p>
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