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Mineral Excretion Associated with EDTA Chelation Therapy

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ABSTRACT: This study measured excretion of 11 minerals induced by EDTA chelation therapy in 25 adults (aluminum, cadmium, calcium, chromium, copper, iron, lead, magnesium, manganese, mercury, zinc). We administered 20 EDTA infusions (3 g, with magnesium and ascorbate) 1 to 2 weeks apart and measured 24-hr urinary excretions of minerals before treatment and after treatments 1, 10, and 20. A modest supplement provided replacement nutrient minerals. Long-term excretion was enhanced about 35% for lead and 60% for cadmium, but not for mercury. Enhanced excretion of essential minerals was small compared to dietary and supplementary intakes. These results support the nutritional safety of EDTA chelation therapy by the protocol used.

Introduction

Intravenous (IV) infusion of ethylenediaminetetraacetic acid (EDTA) is a generally accepted treatment for acute and high-level lead intoxication (1,2). Its possible utility to treat low-level, chronic burden of lead or cadmium is questioned by some due to possible adverse reactions including kidney damage and depletion of essential minerals (3,4). However, these adverse reactions are strongly dependent on the frequency and infusion rate of chelation therapy, which in the past were often higher than those now widely used. We explored the possibility that less intense therapy (5) may prove safe enough to use for

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levels of lead or cadmium intoxication lower than are now generally considered appropriate for IV EDTA treatment. In addition, we sought to document nutrient mineral losses during chelation therapy so that informed decisions can be made about adequate nutritional supplementation.

Because chronic, low-level intoxication with lead and cadmium has been implicated as contributing to the current epidemic of hypertension (6-10), we studied adults with previously diagnosed hypertension and selected those with the largest increase in excretion of lead or cadmium following a challenge infusion of EDTA. We then gave them a total of 20 EDTA infusions spaced at least 1 week apart and modest amounts of replacement minerals in the form of a broad-spectrum, multivitamin and mineral supplement.

We report here measurements of EDTA-induced excretion of 11 minerals during the first 24 hr following entry into the study and following infusions 1, 10, and 20. These measurements appear to be mostly new to the literature and suggest that appropriate EDTA treatment and mineral supplementation can significantly enhance excretion of body lead and cadmium without undue loss of essential minerals. In previous publications from this study we have reported lack of harm (and possible benefit) to kidney function (11), undisturbed blood chemical profile (12), and improved general clinical symptomatology (13).

Methods

Local newspaper and television advertisements solicited volunteers with hypertension for a study of chelation therapy. They were required to be ambulatory, over age 40, have a 1-year history of diagnosed hypertension, and have a blood pressure of at least 140 mm systolic and 90 mm diastolic (average of 3 measurements at least 10 minutes apart). The 127 volunteers were asked to complete screening laboratory work (24-test multichemical profile, complete blood count, urine analysis, blood lead and cadmium, and hair minerals), the Cornell Medical Index (14), history questionnaires, and a challenge chelation with 3 g EDTA and 15 g ascorbate. We selected 25 subjects with normal kidney function (fasting serum creatinine < 1.7 mg/dL) who showed at least a 5-fold increase in 24-hr urinary excretion of lead or cadmium as a result of the EDTA challenge. Nearly all were taking antihypertensive medications, which they were advised to con-

TABLE 1

Urinary 24-hr Excretion and Supplementary Intake of Minerals (25 subjects)

Mineral Unit		#1 Pretreatment Excretion Mean (SD)	#2 Mean Post EDTA Excretion (Treatments 1, 10, 20)	#3 EDTA-Induced Excretion (#2-#1)	#4 Mean Induced Excretion Incl. Non-treatment Days**	#5 Supplement*
Aluminum	mcg	51 (30)	98	47	4.4	
Cadmium	mcg	1.0 (0.6)	7.3	6.3	0.59	
Calcium	mg	157 (90)	340	183	17	250
Chromium	mcg	1.1 (0.7)	1.8	0.7	0.06	200
Copper	mcg	32 (14)	46	14	1.3	2000
Iron	mcg	80 (36)	660	580	54	15000
Lead	mcg	13 (9)	64	51	4.7	
Magnesium	mg	110 (42)	147	37	3.4	219***
Manganese	mcg	0.9 (1.0)	72	71	6.6	5000
Mercury	mcg	1.7 (2.7)	2.1	0.4	0.04	
Zinc	mg	0.65 (0.34)	20	19	1.8	15

*Bronson Insurance Formula; other ingredients include: Phosphorus 250 mg, iodine 150 mcg, molybdenum 100 mcg, selenium 20 mcg, vit. A 7500 IU, vit. D 400 IU, vit. E 40 IU, ascorbic acid 250 mg, thiamin 2 mg, riboflavin 2 mg, pyridoxine, 3 mg, cobalamine 9 mcg, niacinamide 20 mg, pantothenic acid 15 mg, biotin 300 mcg, folic acid 400 mcg, choline 250 mg, inositol 250 mg, PABA 30 mg, rutin 200 mg.

**EDTA-induced excretion (#3), times 20 treatments, divided by 215 d mean duration of treatments.

***Includes 19 mg mean daily intake from 208 mg in each EDTA infusion (19 mg = 208 mg times 20 treatments, divided by 215 d).

tinue. Nine subjects who met our criteria for hypertension during the initial screening tested as normotensive when the treatment phase began. Subjects signed an informed consent form prior to entering the study, which was conducted in keeping with the Helsinki Declaration of 1975.

A series of 20 EDTA infusions (including the initial screening infusion) was administered at intervals of 1 to 2 weeks. The series was completed in 27 to 37 weeks (mean 30.8), as convenient for the sub-

jects. Each infusion contained 3 g disodium EDTA (Keylate: Edetate Disodium: The Key Co., St. Louis, Missouri), 15 g injectable ascorbic acid buffered with sodium bicarbonate (Steris, Inc., Glendale, Arizona), 800 mg injectable magnesium chloride, 40 mg procaine, and 1000 units heparin delivered in 590 mL sterile, deionized water. It was intravenously infused during a period of 3 to 5 hours. Because the goal was to eliminate toxic minerals, but not essential minerals, each subject was given a supply of multivitamin and mineral supplements (Table 1) and instructed to take 3 tablets/day (Vitamin and Mineral Insurance Formula, Bronson Pharmaceuticals, La Canada, California). Eighteen of the 25 subjects reported already taking a multinutrient supplement or individual mineral supplements (primarily calcium, zinc, and magnesium).

A 24-hr urine sample was collected from each subject immediately before and immediately after infusion 1 (the screening challenge) and after infusions 10 and 20; subjects voided prior to infusion and collected for 24 hr. Aluminum, lead, cadmium, and manganese were measured by use of a Perkin-Elmer HGA-500 graphite furnace and model 306 atomic absorption spectrophotometer with deuterium background correction lamp. Calcium, magnesium, iron, copper, and zinc were analyzed on a Perkin-Elmer 560 spectrophotometer. Mercury analysis was performed on a Perkin-Elmer MAS-50A mercury analyzer system by the method of Hatch and Ott (15). Except for mercury, measured values were virtually all at least several times the detection limits and are believed to be accurate. For mercury, 20% of individual measurements were less than the detection limit of 0.05 mcg/24 hr. Means were calculated by setting these values equal to half of the detection limit; because these means are 40 times the detection limits, they, too, are judged to be accurate.

Results

The 24-hr urine samples collected after the first treatment showed markedly higher amounts of nearly all minerals tested than did the pre-infusion samples (Figures 1-5). Only mercury showed no statistically significant initial increase ($p > 0.05$ by paired t-test). There was a 7-fold increase in mean 24-hr excretion for lead and cadmium, and a nearly 2-fold increase for aluminum following the first chelation. Among the essential minerals the largest 24-hr increases occurred for manganese (50-fold), zinc (30-fold), iron (8-fold), and cal-

FIGURE 1

Urinary excretion of lead and aluminum (mean ± SD), 24-hr samples before treatment and after infusions 1, 10, and 20. Only small amounts of chelation-induced mineral excretion occur after the first 24 hr. To avoid overcrowding, some SDs (a measure of group variability) are shown on only one side of the means. Tbe increased excretion of aluminum approximately equals amounts found in the infused solution. Because the distributions of excretions are often asymmetrical (skewed toward high excretion), most subjects bad excretions less than the means shown, and the ranges ± 1 SD do not necessarily have the same significance that they do with Gaussian distributions.

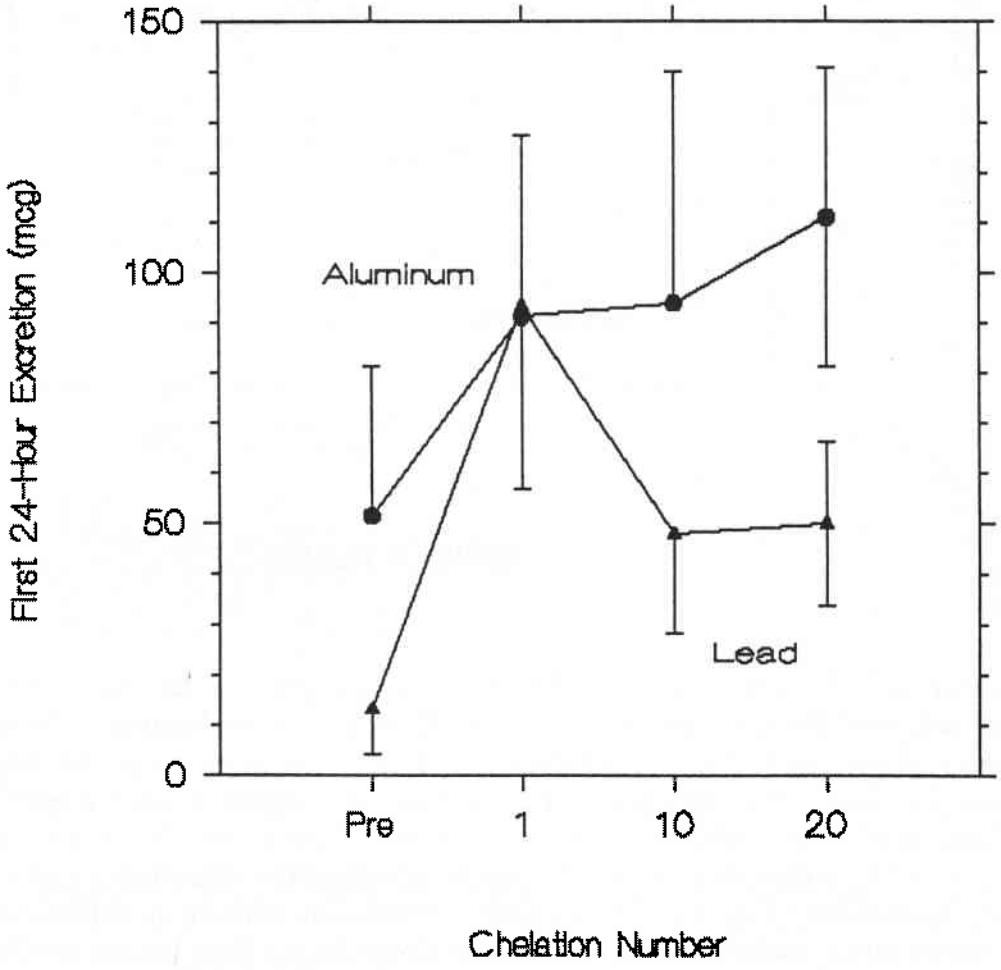
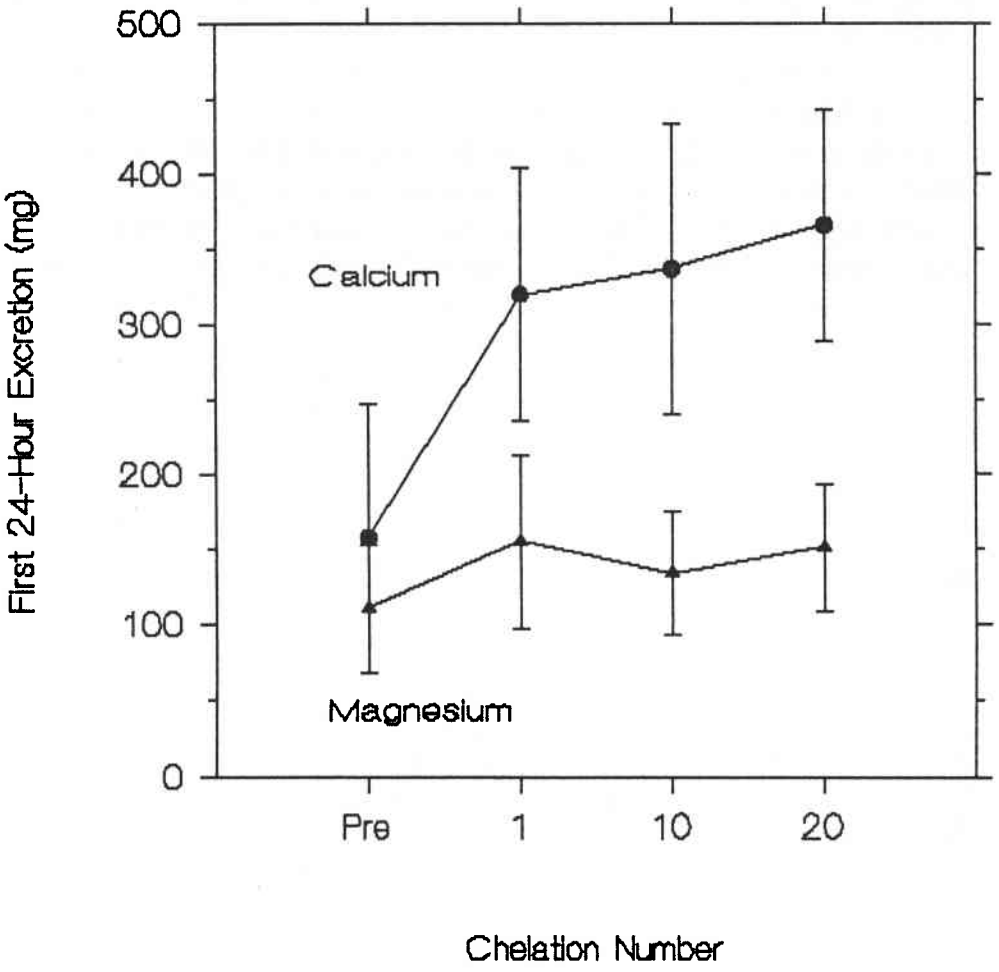


FIGURE 2

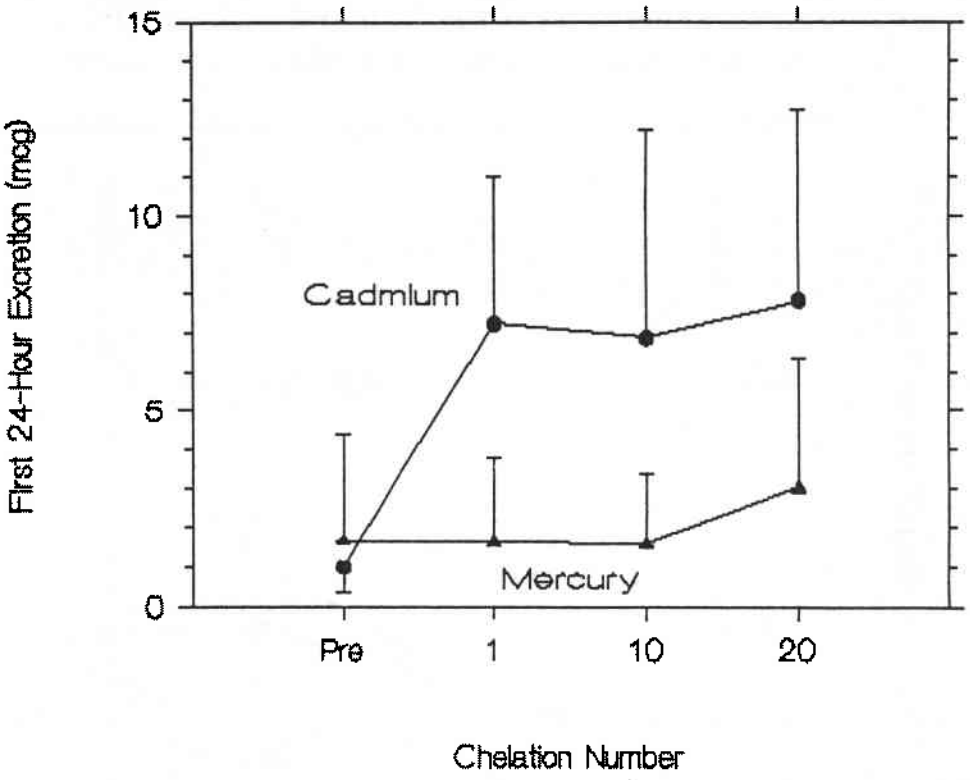
Urinary excretion of calcium and magnesium.



cium (2-fold). These increased excretions during the 1st 24 hr were maintained throughout the study for all minerals including cadmium but *not* for lead (Fig. 1), which dropped by nearly one half between the 1st and 10th infusions ($P < 0.0001$ by paired t-test, 2-tailed). Magnesium excretion may have declined during the same interval ($P = 0.03$), but the decline was small and was not maintained at the 20th infusion (Fig. 2). Unlike lead, aluminum showed a substantial rise in mean 24-hr excretion between the 1st and 20th infusions (Fig. 1, $P = 0.02$; see discussion). Mercury excretion appeared to increase at the 20th infusion (Fig. 3, $P = 0.03$).

FIGURE 3

Urinary excretion of mercury and cadmium.

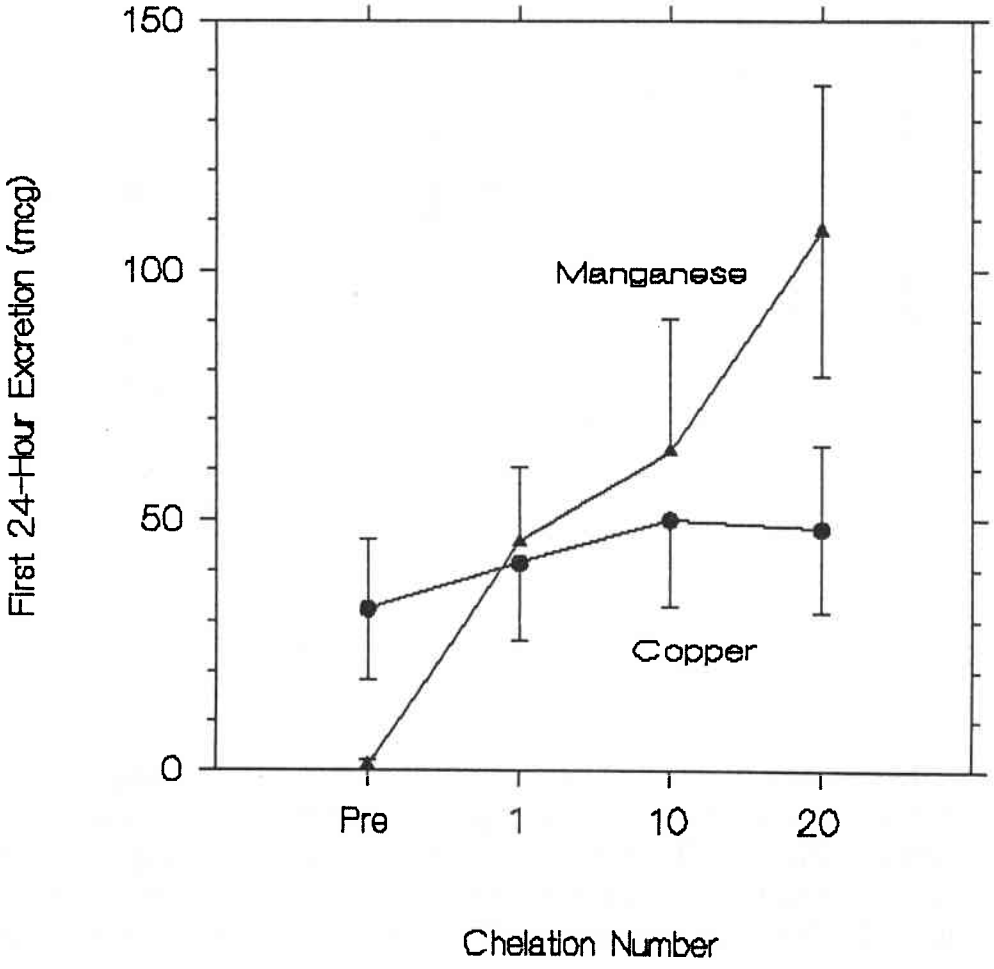


The nutrient minerals manganese and chromium also showed statistically significant increases after many infusions, especially manganese (Fig. 4). These delayed increases and the suggestive rise for calcium may represent a previously unreported consequence of repeated EDTA treatments, or they may be due entirely or in part to our supplementation with these minerals. This question could be studied by repeating our experiment without mineral supplements.

Table 1 summarizes the excretion measurements and shows approximate lower limits for the extra mineral excretion induced by the 20 EDTA infusions. The amounts are lower limits because of the small, unmeasured amounts of EDTA-induced excretion that may occur following the first 24hr after each infusion, according to available information for lead (5,16,17), calcium (16,18), zinc (16,19) and other minerals (16). Table 1, column #1 shows 24-hr mean excretions before treatment. Columns #2 and #3 reflect mean excretions during

FIGURE 4

Urinary excretion of manganese and copper. The increased excretion of manganese at the 10th and 20th chelations might be due, all or in part, to the supplement given.

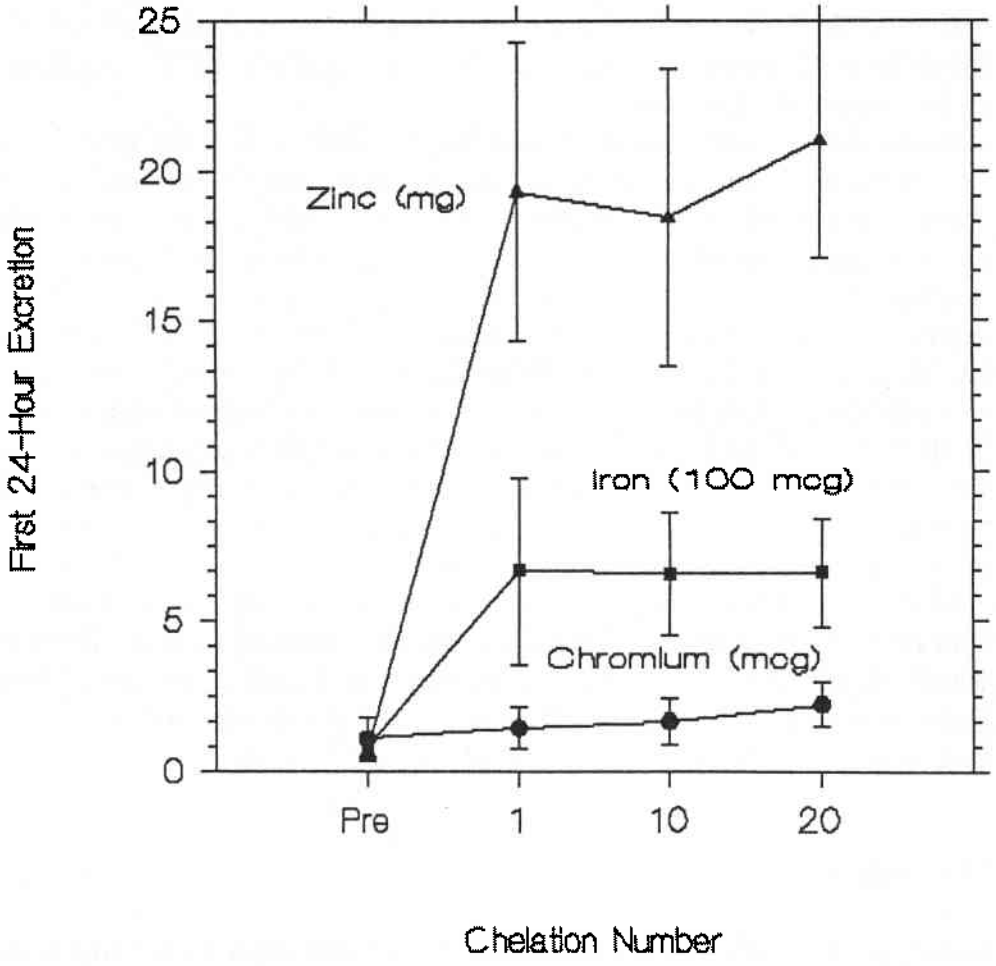


the first 24 hr following treatments 1, 10, and 20. Column #4 shows the net EDTA-induced excretion, *time-averaged to include the non-treatment days.*

For the toxic minerals shown in Table 1, column #4 shows the following approximate *time-averaged* increases over pretreatment excretions: lead 35%, cadmium 60%, aluminum 10% and mercury 0% (smaller than the 1st 24-hr increases due to inclusion of non-treatment days). The corresponding time-averaged increases for nutrient

FIGURE 5

Urinary excretion of zinc, iron, and chromium.



minerals were in a comparable range except for manganese and zinc, for which EDTA-induced excretions were respectively about 7- and 3-fold greater than baseline excretion. However, in absolute amounts the EDTA-induced excretions of manganese, zinc and all other essential minerals shown in column #4 were much smaller than usual dietary intakes and absorptions (20).

Similarly, the supplements given (Table 1, column #5) were much larger than the induced excretions: 9-fold larger for zinc, 15-fold for calcium, and 65- to 3000-fold for the other nutrients studied. These margins appear ample to compensate for the incomplete absorption of

essential minerals. For example, about 15% to 40% of food zinc is absorbable, depending in part on zinc status (20). Hence, supplementation with these modest amounts of essential minerals afforded our subjects good protection against depletion during EDTA treatments at 1- to 2-week intervals.

Mean 24-hr excretion of lead after the first EDTA infusion was 93 mcg (range, 23 to 166 mcg), much less than the 1200 mcg/3 g EDTA currently considered to indicate increased lead burden and risk of chronic lead nephropathy (8). Initial mean blood lead level was 6.8 mcg/dL (range, 2 to 12 mcg/dL); 50 mcg/dL is the current U.S. Department of Labor maximum permitted level (occupational safety and health standard 1910.1025). After 20 EDTA treatments, mean blood level declined 45% to 3.7 mcg/dL, $P = 0.000$ by paired t-test).

Mean initial 24-hr cadmium excretion was 7 mcg (range, 1.6 to 18 mcg), and mean initial blood cadmium was 0.09 mcg/dL (range, 0.02 to 0.21 mcg/dL). After 20 EDTA treatments, mean blood level was 0.11 mcg/dL, an insignificant increase.

Group average blood pressures did not change in a consistent direction or more than 2 mm during the study. Because nearly all subjects were taking antihypertensive medications, further studies of hypertension may be warranted with subjects not taking such medications and with those having higher levels of toxic metals.

Discussion

This report is intended to provide new information about the urinary loss of essential minerals during EDTA infusion therapy, one of the major concerns about the safety of this therapy. Although generalization from our findings may be limited by being derived from selected, hypertensive subjects, our data seem unlikely to differ broadly from excretions in other populations receiving medical treatment with EDTA infusions. Tbe previously published excretion data of which we are aware are all based on analytical capabilities of 30 years ago, and are limited primarily to calcium (18) and zinc (19). Another early study (16) focused on several other minerals (including non-nutrient ones) but was hampered in some cases by inadequate analytical sensitivity. None of these studies dealt with repeated EDTA infusions spaced 1 to 2 weeks apart.

In agreement with prior studies, we found that EDTA infusions increase urinary excretion of all toxic and essential minerals studied

except mercury. However, under the conditions of our experiment, the increased excretions of essential nutrients were all small compared to usual dietary intakes and absorptions. The most significant EDTA-induced loss in our experiment is presumably the average 1.8 mg/day of zinc. This may be compared to typical daily intakes of 10 to 15 mg/day (20), and to the amount in the supplement we used.

For all other essential minerals studied, EDTA-induced excretions were smaller than for zinc, relative to dietary intakes and supplementary amounts. We conclude that there is negligible risk of depleting the studied nutrients during EDTA chelation therapy with 3 g EDTA at intervals of 1 week or more, when used with modest levels of mineral supplementation. Further studies are needed to assess other minerals such as selenium and molybdenum, and other subjects who might differ significantly from our selected population.

More frequent EDTA infusions than we used would increase urinary loss of essential minerals but probably not in full proportion to EDTA dosage. With *daily* infusion of 3 g EDTA, induced losses of zinc might approach 15 mg/d in addition to usual non-induced losses. If so, prolonged treatment would risk zinc depletion even with a 15 mg/d supplement because absorption is never complete. Calcium depletion might occur as well, if it were not adequately supplemented. Further studies would be required to assess mineral balance with higher intensity EDTA treatments than we used.

Besides nutrient mineral depletion, two major concerns have been expressed regarding IV EDTA therapy. One is the fear that this technique may impair renal function. In earlier reports we, as well as others, have presented measures of renal function which indicated no renal impairment, and perhaps even a benefit if treatments are appropriate in composition and administration (11,21-23). Tbe other concern has been that EDTA chelation invites a metabolic upheaval either directly or indirectly through the loss of essential minerals. We have demonstrated the lack of general metabolic upheaval in previous reports which show overall stability in the usual 24-test multichemical profile (12) and complete blood count.

The observed doubling of aluminum excretion after EDTA treatment puzzled us (Figure 1). Because of uncertainty as to whether EDTA is an effective aluminum chelator under physiologic conditions, we speculated that the infused solution might contain sufficient aluminum to account for the observed increases which averaged about 40 to 60 mcg/24 hr. Analysis of later stocks of various components of the infused solutions showed negligible aluminum except in

the buffered ascorbic acid solution. It contained about 52 mcg per treatment (26 mcg per 30-mL bottle; duplicate analyses of two samples of one lot by our lab and by Monroe Laboratories, Southfield, New York). Because this amount is similar to the observed average increase in aluminum excretion, the increase migbt not represent removal of body stores of aluminum.

The manufacturer of our buffered ascorbic acid suggests that this amount of aluminum is of minimal concern and may originate from tbe glass container or rubber seal. The amount is much less than typical oral intakes from widely used food additives and foods—about 30 mg/d according to Bjorksten (24). However, it might not be large compared to typical daily aluminum *absorption*, as suggested by our observation of increased aluminum excretion after many treatments. Further consideration seems desirable for injectable solutions that are to be used repeatedly in the same individual. Recent communications from the manufacturer suggest cause for optimism regarding the possibility of virtually aluminum-free injectable ascorbate by early 1990.

Previously there has been little information available about excretion of essential minerals during IV EDTA chelation therapy. This lack made it difficult to evaluate the nutritional safety of such therapy and prevented well informed decisions about adequate supplementation. We have attempted to supply some of the needed information for treatment programs similar to the one used here.

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