Urinary excretion of meso-2,3-dimercaptosuccinic acid in human subjects

The urinary excretion of meso-2,3-dimercaptosuccinic acid (DMSA), which is an effective chelating agent for lead, was determined after the oral administration of 10 mg DMSA/kg to six normal young men. The DMSA that was absorbed was extensively biotransformed. After 14 hours only 2.53% of the administered DMSA was excreted in the urine as unaltered DMSA and 18.1% as altered forms. The unaltered DMSA was 12% of the total DMSA found in the urine. The altered form(s) of DMSA was 88% of the total urinary DMSA. The altered DMSA can be converted to unaltered DMSA by electrolytic reduction, which indicates that the altered forms of DMSA are disulfides. The excretion of altered DMSA reached a peak between 2 and 4 hours after DMSA administration. There were small but statistically significant increases in the excretion of zinc, copper, and lead after DMSA administration. DMSA did not influence the urinary excretion of 27 other metals and elements. (CLIN PHARMACOL THER 1989;45: 520-6.)

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There is continuing concern about the cumulative effect of lead in human beings, especially in children between the ages of 6 months and 5 years.[1-4] Along with this concern, there has been a continued search for therapeutically more potent and less toxic metal-binding or chelating agents to mobilize and to increase the excretion of body lead in human subjects.[5-8] Compounds that have been used to accomplish this in the past have included $CaNa_2EDTA$,[9] dimercaprol (BAL),[9] a combination of these two agents,[10] D-penicillamine,[10] 2,3-dimercapto-1-propanesulfonic acid (Unithiol, Dimaval, DMPS)[8,11] and, most recently, the water-soluble and less toxic analogue of dimercaprol, meso-2,3-dimercaptosuccinic acid (DMSA).[5,7]

Comprehensive reviews of DMSA (which is classified by the FDA as an orphan drug) and chemically analogous dimercapto metal-binding agents have been done previously.[12,13] Of these compounds, the most promising for the treatment of chronic or acute lead intoxication in human subjects appears to be DMSA because of its effectiveness in mobilizing lead in men[7] and children[14] and because of its relatively low toxicity.[12,15,16] Neither adverse effects nor kidney disease have been shown to result from its use. Eighteen men and fifteen children with elevated blood lead levels were treated with DMSA for 5 days by Graziano et al.,[7,14] who concluded that DMSA appears to be very promising and, because it can be given by mouth, it may greatly simplify the treatment of lead intoxication. In addition, Cory-Slechta[17] has shown that, in rats, DMSA mobilizes Pb only from soft tissue without redistribution. This is in contrast to $CaNa_2EDTA$, which mobilizes and redistributes Pb to target organs, such as the brain.[18] It is becoming disturbingly apparent that many of the older chelating agents, such as $CaNa_2EDTA$ and British antilewisite, increase the level of toxic metals in the brain.

Data on the excretion kinetics of DMSA and its metabolites and on the identity of its metabolites in the urine have been scant and, in the case of human subjects, completely absent. Animal studies have used radioactive DMSA[19,20] because of the lack of other sen-

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sitive methods of analysis. A highly sensitive and accurate fluorescent method for the determination of dimercapto compounds in the urine has been developed by Maiorino et al.[21,23] The method has made metabolic studies of DMSA in human subjects feasible, without the use of radioactive DMSA. This article presents the findings of experiments in which six healthy young men were given 10 mg DMSA/kg orally, and the urinary excretion of DMSA, its metabolites, and metals such as lead, copper, and zinc was determined. Although the study of lead, copper, and excretion was not the original purpose of these experiments, it was possible to include them in the study because the urine samples were collected and stored in metal-free containers.

MATERIAL AND METHODS

Chemicals. Meso-DMSA, 110 mg per hard gelatin capsule, was a gift of Johnson & Johnson Baby Products (Skillman, N.J.). The capsules were opened and analyzed for DMSA by means of the bromobimane assay for dithiols before and after electrolytic reduction. They were found to contain at least 96% unaltered DMSA. The amount of oxidized DMSA was less than 4%. D-penicillamine and the Na salt of 2,3-dimercaptopropane-1-sulfonic acid (DMPS, Dimaval) were gifts of Heyl (West Berlin). N-(2,3-dimercaptopropyl)phthalamidic acid (DMPA) was obtained from the Medicinal Chemistry Department of the Walter Reed Army Institute of Research. Monobromobimane (mBB, Thiolyte) was purchased from Behring Diagnostics (LaJolla, Calif.). All other chemicals and their sources have been described previously.[21,23]

Human protocol. Six normal, healthy young men between 22 and 31 years of age were fasted for 11 hours. A zero time urine sample was collected; immediately afterward DMSA was given orally with distilled water. The dose of DMSA was 10 mg/kg, rounded off to the nearest 110 mg because each capsule contained 110 mg DMSA. This dose was selected because it was the lowest dose used in a published clinical study,[7] and it was not expected to be toxic. Urine was collected for an 8-hour period before DMSA administration in order to get a baseline lead-excretion value. Urine was also collected at 1, 2, 4, 6, 9, and 14 hours for the measurement of DMSA, its metabolites, and the metals Pb, Cu, and Zn. After the 4-hour urine collection, each subject consumed a turkey sandwich. After the 9-hour collection, each subject ate two turkey sandwiches. A blood sample was withdrawn before DMSA administration and after the 14-hour urine collection. Vital signs were determined and recorded at zero time and at 14 hours. This study was approved by the Human Subjects Committee of the University of Arizona.

HPLC analysis. The principle on which the determination of DMSA is based consists of the conversion of DMSA in the urine to a highly fluorescent and stable derivative, which is separated by ion-interaction HPLC and is detected by fluorescence. This is accomplished by the reaction between the sulfhydryl groups of DMSA and the methylene bromide moiety of mBB in aqueous solution at pH 8.3.[21,23] *Unaltered DMSA* in the urine is determined by the direct analysis of a urine sample by this method. *Total DMSA* (unaltered + altered) is determined by the same method except that a sample of the urine first undergoes electrolytic reduction,[23] after which it is immediately derivatized with mBB and is then continued through the analytical procedure. *Altered DMSA* is obtained by subtracting unaltered DMSA from total DMSA. Altered DMSA represents DMSA disulfides and mixed disulfides of DMSA with cysteine, reduced glutathione (GSH), and other thiols. Quantification is accomplished by adding DMSA standards to urine samples that were collected before drug administration (blanks) and treating them in the same manner as the urine samples collected after DMSA administration. The urine samples of each subject were assayed with DMSA standards that encompassed the range of DMSA concentrations in the urine samples collected after DMSA administration.

Determination of metal concentrations. Concentrations of the following metals were determined by use of an Instrumentation Laboratory Video 12 atomic absorption spectrophotometer (Allied Analytical Systems, Menlo Park, Calif.). The concentration of copper in urine was determined by graphite furnace atomic absorption spectrometry (GFAAS) and that of zinc was determined by flame atomic absorption spectrometry (FAAS).[22] Lead concentration was determined by GFAAS. For the lead determinations, urine aliquots were diluted 10-fold with a 1% solution of ammonium dihydrogen phosphate in 0.2N HNO_3, then aspirated into a graphite cuvette for 6 seconds (temperature, 100° C). The temperature was ramped to 550° C over 15 seconds and then to 800° C over 20 seconds to complete the ashing process. Peak height integration of the signal was initiated just before atomization at 2100° C. Background correction was performed by operation of the lead hollow cathode lamp in the Smith-Hieftje mode with detection at 283.3 nm. Findings were recorded directly in ng/ml Pb after instrument calibra-

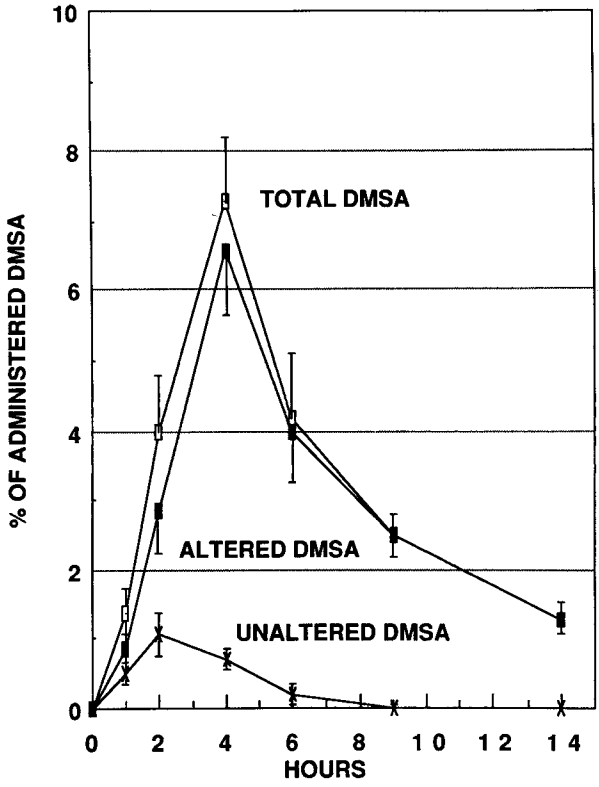

Fig. 1. Urinary excretion of total, altered, and unaltered DMSA (expressed as a percentage of administered DMSA) by six normal men. A single dose of DMSA (10 mg/kg) was given orally after 11 hours of fasting. Error bars indicate SEM.

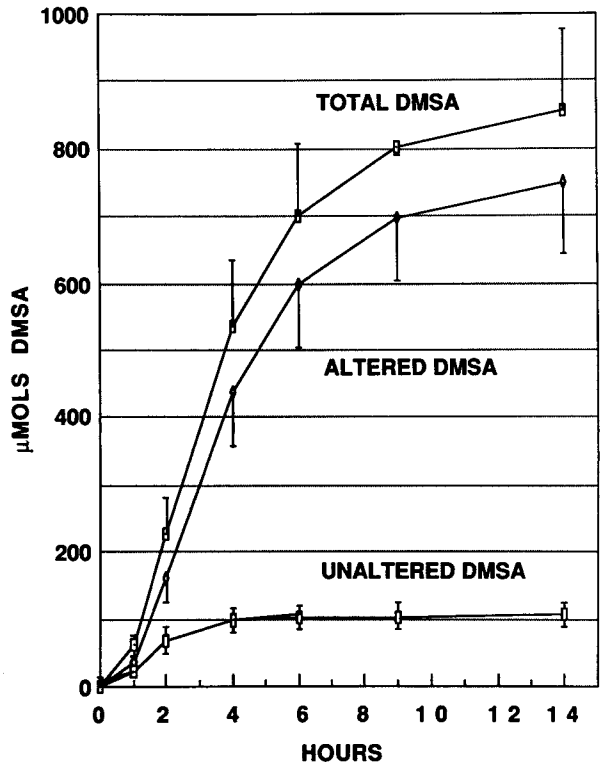

Fig. 2. Cumulative urinary excretion of total, altered, and unaltered DMSA by six normal men given a single oral dose of 10 mg DMSA/kg after 11 hours of fasting. Error bars indicate SEM.

tion, with lead standards between 25 and 200 ng/ml Pb. The precision of the copper and zinc analyses was determined by comparison with a sample of the National Bureau of Standards (NBS) SRM-1549 nonfat dry milk prepared in a manner identical to that used for the urine samples. The NBS values are 700 ± 100 ppb Cu and 46.1 ± 2.2 ppm Zn. Our values were 609 ± 55 ppb Cu and 45.0 ± 3.2 ppm Zn. The accuracy of the lead method was tested by analysis of freshly voided urine to which known amounts of lead chloride (J.T. Baker, Phillipsburg, N.J., 99.9% purity) were added for final concentrations of 28.5, 68.4, and 142.5 ppb lead (not accounting for endogenous Pb). The percentage deviations from the nominal concentrations were −7.0, −5.3, and −1.1, respectively (after subtraction of the blank urine lead value). Inductively coupled plasma emission (ICPE) spectrometric analysis of other metals in the 1-hour and 4-hour urine samples was performed by Doctors Data Laboratories Inc. (West Chicago, Ill.).

Collection, processing, and storage of urine. Urine was collected in Pyrex ground-glass stoppered graduated cylinders that had been rinsed with 25% HNO_3 and with double-distilled water to remove residual metals. After collection, the urine was mixed immediately by gentle inversion of the cylinder five times. Aliquots were removed, treated with mBB, and stored at −20° C until thawed for the determination of unaltered DMSA. Another sample of the urine was stored in a 50 ml polypropylene tube at −20° C until analyzed for total DMSA, copper, lead, zinc, and other metals.

Other procedures. Blood samples were analyzed for lead by the SmithKline Bio-Science Laboratory (Los Angeles, Calif.). Other clinical chemistry determinations on blood samples were performed by the University Hospital Department of Pathology.

Cupruretic activity in rats. Male rats (Hansen Sprague-Dawley Inc., Indianapolis, Ind.), after a 7-day quarantine, were placed in plastic metabolism cages for 2 days to adapt. After this time they weighed about 200 g, and they were divided into groups of four and given distilled water by gastric lavage twice a day for 2 days.

The chelating agent was given at a level of 1 mmol/kg each time twice a day for 4 days by gastric lavage. All animals on whom gastric lavage was performed were fasted for 16 hours (overnight). The next morning at 9 AM the chelating agent was given by gastric lavage. Food was made available from 10 AM to noon. The animals were then fasted until 1 PM, when gastric lavage was again performed. Food was made available at 2 PM and again removed at 5 PM. Urine was collected each day, and appropriate areas of the metabolism cages were rinsed with distilled water. The urine and rinsings were quantitatively transferred to a volumetric flask and diluted to 25.0 ml with distilled water. Rats were given water and LabBlox food (Teklad, Madison, Wis.), ad libitum.

RESULTS

Clinical. During the testing period, no clinically significant drug-related changes from baseline values were found in the blood of any subject, according to the clinical laboratory results. All the lead levels of blood taken both before and after the 14-hour testing period were within the normal limits. The range was from 3 to 11 μg Pb/dl. All subjects remained asymptomatic, although one subject did complain of a low backache. He was the only subject to report any complaints. He noted low backaches and bilateral flank aches during the day the drug was ingested. There were no associated symptoms, such as dysuria, frequent urination, diarrhea, constipation, abdominal pain, nausea, or vomiting. Repeated physical examinations performed during the episodes showed no abnormalities, such as fever or tenderness.

Urinary excretion of DMSA, Zn, Cu, and Pb. The urinary excretion of unaltered DMSA reached a peak before that of altered DMSA (Fig. 1). A plot of the cumulative excretion (Fig. 2) showed that by 14 hours after administration of DMSA, the total (856 ± 131 μmol), altered (751 ± 116 μmol), and unaltered (105 ± 20 μmol) DMSA excreted in the urine represented 20.6% ± 2.4% SEM, 18.1% ± 2.1% SEM, and 2.53% ± 0.40% SEM of the administered DMSA, respectively. By 14 hours after administration most of the total DMSA in the urine was in an altered form (88%). The altered DMSA appeared to be in the form of disulfide(s) because it was converted to unaltered DMSA by electrolytic reduction. About 12% of the total DMSA in the urine was found in its unaltered form.

The excretion of Zn, Pb, and Cu in the urine reached a peak at 4 hours after DMSA administration (Fig. 3) and coincided with the peak of altered DMSA excretion (Fig. 1). The second rise in the Zn curve (Fig. 3) 6 hours after DMSA ingestion is presumed to be caused by the intake of food after the 4-hour and 9-hour urine collections. The urinary Cu, Pb, and Zn excretions (Fig. 3) were compared by linear regression analysis to the urinary excretion of total DMSA (Fig. 1). The significant correlation coefficients for total DMSA versus Cu, Pb, and Zn were 0.942, 0.603, and 0.594, respectively. The 9-hour and 14-hour time points were excluded for Zn. The cumulative urinary excretion of Pb by 6 hours after DMSA administration exceeded the urinary excretion of Pb collected for an 8-hour period before DMSA administration by a factor of 4. The values were 147 pmol ± 10.1 pmol SEM and 39 pmol ± 9.5 pmol SEM, respectively.

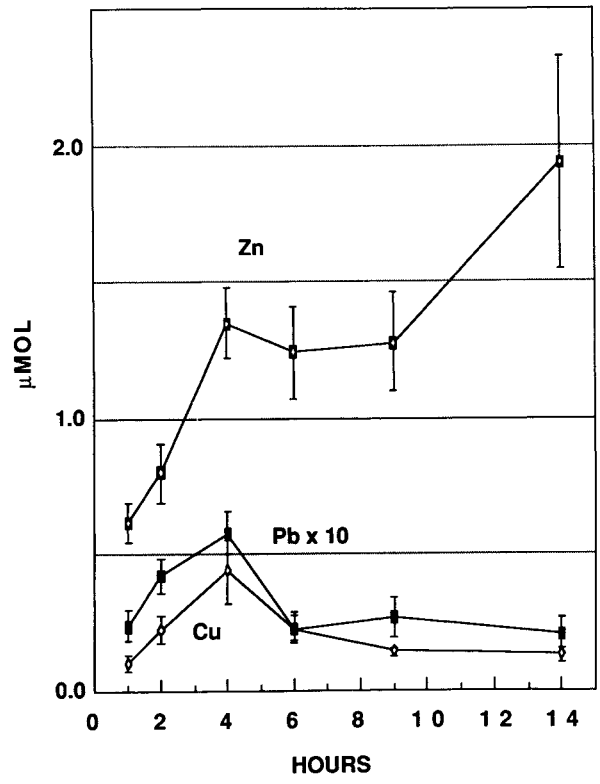

Fig. 3. Urinary excretion of Zn, Pb, and Cu by six normal men who were given a single oral dose of 10 mg DMSA/kg after 11 hours of fasting. Error bars indicate SEM.

Urinary excretion of other minerals. The excretion of 28 minerals after DMSA administration was examined by comparing the μmol/hour found in the urine samples collected at 1 hour and 4 hours (Table I). Statistically significant differences were not found for the excretion of the minerals listed in Table I between the two time collections as determined by one-way ANOVA, except that when the 1-hour urine samples were compared with the 4-hour samples, the Na ex-

Table I. Excretion of minerals in the urine after administration of DMSA to six normal men

	Urines were collected between	
	0-1 hr	*2-4 hr*
Elements	*(μmol/hr ± SEM)*	
Boron	16.3 ± 3.2	12.9 ± 2.5
Calcium	120 ± 21	128 ± 24
Iron	0.078 ± 0.011	0.085 ± 0.028
Lithium	0.24 ± 0.04	0.15 ± 0.03
Magnesium	105 ± 25	95.5 ± 12.1
Phosphorus	663 ± 157	816 ± 145
Potassium	3462 ± 197	4642 ± 803
Silicon	21.4 ± 6.5	16.6 ± 4.8
Sodium	5577 ± 1034	7310 ± 1434
Strontium	0.078 ± 0.011	0.088 ± 0.017
Tin	0.22 ± 0.05	0.16 ± 0.02

The levels of arsenic (0.07), selenium (0.004), mercury (0.080), cadmium (0.020), aluminum (0.040), nickel (0.300), beryllium (0.005), manganese (0.005), chromium (0.030), cobalt (0.020), molybdenum (0.100), vanadium (0.030), barium (0.005), gold (0.020), silver (0.020) and zirconium (0.040) in 1-hour and 4-hour urine samples were examined and found to be either below or at the limit of detection of the inductively coupled plasma emission. The levels of detection (ppm) are given in parentheses after each element in the preceding sentence.

cretion per hour was found to be different at a significance level of $p < 0.005$.

Relative cupruretic activity of chelating agents in rats. In the present studies there was an increased excretion of Cu after DMSA administration (Fig. 3). DMSA and the chemically analogous DMPS have been used by different investigators in carefully controlled human studies that deal with the treatment of lead intoxication,[7,8] as well as for the treatment of Wilson's disease.[24] Therefore, four of the most important chelating agents have been compared in normal rats (Table II) with respect to their relative activity in mobilizing Cu. D-penicillamine has been the drug of choice for treating Wilson's disease since the original studies by Walshe.[25] The findings (Table II) clearly show that, of the dimercapto chelating agents, DMPS is the most effective in mobilizing Cu, but it is still only 71% as effective as the monomercapto compound, D-penicillamine.

DISCUSSION

Studies of the biotransformation and metabolic fate of DMSA have been limited in the past to tracking radioactivity after the administration of ^{14}C-DMSA. McGown et al.[20] showed that 96 hours after oral administration of ^{14}C-DMSA (0.16 mmol/kg) to four male juvenile monkeys *(Macaca mulatta),* approximately

Table II. Urinary excretion of copper after administration of chelating agents to rats

*Compound tested**	*No. of determinations*	*Urinary Cu (μg/24 hr ± SEM)*
Saline	64	3.74 ± 0.33
D-Penicillamine	16	45.36 ± 1.58
DMPS	16	32.82 ± 2.89
DMSA	16	17.92 ± 0.58
DMPA	16	17.74 ± 1.15

*1 mmol/kg given orally twice a day to male rats.
$p < 0.001$ when each treated group is compared with the untreated group.

18% of the administered radioactivity was recovered in the urine, 65% in the feces, and 2% in the expired air. The urine value was similar to that found in human subjects in the present study. When radioactive DMSA (1.0 mmol/kg) was given orally to hamsters, however, 81% of the radioactivity was recovered in the urine within 96 hours.[20] This suggested a species difference between the monkey and the hamster. (Whether the monkeys and hamsters were fasted is unclear.) It was concluded that most, if not all, of the carbon chain of DMSA was excreted intact by the hamster and that the sulfhydryls were oxidized. The extent of the oxidation in vivo and the identity of the oxidized products could not be determined.

The first conclusion that can be drawn from the results of the present experiments is that when DMSA is given orally to normal human subjects, only 20.5% of the administered DMSA could be accounted for in the urine. Of the DMSA administered, only 2.5% was excreted in the urine as unaltered DMSA, and 18% was excreted as altered form(s). Thus the DMSA that was absorbed was extensively biotransformed.*

This left about 80% of the DMSA dose unaccounted for. Two possibilities are apparent. The first possibility is that only about 20% of the DMSA is absorbed from the gastrointestinal tract and 80% is excreted via the feces, which suggests that the male human being and the male juvenile monkey may be similar in their limited ability to absorb DMSA from the gastrointestinal tract. The second possibility is that part or all of the unaccounted for 80% was excreted in the urine in a form that was not subject to electrolytic reduction.

As indicated by the present experiments, after inges-

*The altered DMSA appears to consist of one or more oxidized species, with the major constituent being a mixed disulfide that consists of two cysteine molecules per DMSA molecule.[26] It appears that each S atom of DMSA formed a disulfide linkage with the S atom of one cysteine molecule.

tion of DMSA (Figs. 1 and 2) almost all of the DMSA that is excreted in the urine is in its biotransformed or altered form. Approximately 90% of DMSA found in the urine is altered. Only a very small percentage is found in the unaltered form. Yet numerous investigators have written that one of the important properties of an effective chelating agent is that it should not be metabolized. DMSA is a very effective chelator and is metabolized. It would be of interest, however, to determine whether DMSA, per se, is the metal-mobilizing agent in vivo or whether it is a pro-drug that is biotransformed into a more active metal-mobilizing agent. Dimercaprol, when given to rabbits, is biotransformed to a dithiol found in the urine.[27] The dithiol is different from dimercaprol and, when tested in vitro, was found to be effective against the arsenical, lewisite.

The in vivo site(s) for the biotransformation of DMSA is, at present, unknown. The biotransformation certainly begins by at least 1 hour after DMSA administration (Fig. 1,2). Because of the extensive biotransformation of DMSA, therefore, it might be of value to reevaluate the results of the whole-body autoradiographic distribution studies of ^{14}C-DMSA in mice.[28]

The urinary excretions of Zn, Cu, and Pb were definitely increased after DMSA administration (Fig. 3). This has also been shown by Graziano et al.[7] in men with elevated blood lead concentrations. The correlation of urinary DMSA excretion with urinary Zn, Cu, and Pb excretion, however, has never been demonstrated. Most attempts at correlating DMSA to urinary metal excretion have involved comparison of the dose-response of the administered DMSA with the amount of metal excreted in the urine. We have demonstrated that the increase in Zn, Pb, and Cu excretions (Fig. 3) are highly correlated to the excretion of total DMSA (Fig. 1). This gives greater credence to the direct influence of DMSA on chelation of these metals. By 14 hours after administration, the amounts of Zn, Cu, and Pb excreted in the urine were 7.21 ± 0.75 μmol, 1.27 ± 0.25 μmol, and 0.20 ± 0.016 μmol ± SEM, respectively. The magnitudes of these increases are so small that they do not appear to be of clinical significance, especially since they are the result of the administration of a single dose of DMSA. Five-day regimens of DMSA, however, did not cause a significant increase in the urinary excretion of Zn, Cu, Fe, or Ca in children with elevated blood levels of Pb.[14]

By 14 hours after administration the amounts of total, altered, and unaltered DMSA found in the urine were 856 ± 131 μmol, 751 ± 116 μmol, and 105 ± 20 μmol ± SEM, respectively. This indicates that the Zn, Cu, and Pb chelates of DMSA represented a very small fraction of the total or altered DMSA excreted in the urine. The urinary excretion of other metals and elements (Table I) did not appear to be influenced by DMSA.

As yet, methods for the determination of DMSA concentration in blood have not been developed because of the problems associated with adsorption on and bonding with constituents of blood. Until such methods are available, the findings of this study, which dealt with the kinetics of the appearance of DMSA and its metabolites in the urine, will give an indication of how long it takes for DMSA, its metabolites, or both to be removed from the human body.

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