Urinary mercury after administration of 2,3-dimercaptopropane-1-sulfonic acid: correlation with dental amalgam score

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ABSTRACT **There is considerable controversy as to whether dental amalgams may cause systemic health effects in humans because they liberate elemental mercury. Most such amalgams contain as much as 50% metallic mercury. To determine the influence of dental amalgams on the mercury body burden of humans, we have given volunteers, with and without amalgams in their mouth, the sodium salt of 2,3-dimercaptopropane-1-sulfonic acid (DMPS), a chelating agent safely used in the Soviet Union and West Germany for a number of years. The diameters of dental amalgams of the subjects were determined to obtain the amalgam score. Administration of 300 mg DMPS by mouth increased the mean urinary mercury excretion of the amalgam group from 0.70 to 17.2 μg and that of the nonamalgam group from 0.27 to 5.1 μg over a 9-h period. Two-thirds of the mercury excreted in the urine of those with dental amalgams appears to be derived originally from the mercury vapor released from their amalgams. Linear regression analysis indicated a highly significant positive correlation between the mercury excreted in the urine 2 h after DMPS administration and the dental amalgam scores. DMPS can be used to increase the urinary excretion of mercury and thus increase the significance and reliability of this measure of mercury exposure or burden, especially in cases of micromercurialism. —Aposhian, H. V.; Bruce, D. C.; Alter, W.; Dart, R. C.; Hurlbut, K. M.; Aposhian, M. M. Urinary mercury after administration of 2,3-dimercaptopropane-1-sulfonic acid: correlation with dental amalgam score. *FASEB J.* 6: 2472–2476; 1992.**

Key Words: dental amalgam toxicity • amalgam • mercury toxicity • amalgam score • teeth • urinary • mercury

CONTROVERSY HAS AGAIN ARISEN as to the health hazards of elemental mercury vapors evolving from "silver" dental amalgams (1–9). At the present time, the evidence that mercury vapor is released from amalgams is formidable (for reviews see refs 1, 4, 9, 10, 11). This has been supported by experiments in which amalgams containing radioactive metallic ^{203}Hg were placed in the teeth of sheep (5). Criticisms (12–14) of the latter experiments (5) have been lessened to some extent after the experiments were repeated in a monkey with essentially the same results (6). Calculations based on experimental determinations of the intra oral air of humans indicate that mercury vapor is not only released from dental amalgams but it is also absorbed (1, 4–8). The vapor readily enters the blood and is transported to and taken up by the brain and other tissues. In both the blood and tissues it is oxidized to mercuric mercury (Hg^{2+}). Of all the tissues, the greatest accumulation of inorganic mercury is in the kidney (3, 11, 15, 16).

Mercury vaporization at the surfaces of amalgam fillings appears to be generated mainly by the friction caused by occlusion and by the contact of food with amalgam surfaces. The release of mercury vapor from dental amalgams under various conditions such as brushing, chewing, and drinking is now generally accepted. "Silver" dental amalgams are complex metal alloys. For example, one of the most frequently used dental amalgams in the Tucson, Arizona area consists of 47.3% metallic mercury and 52.7% alloy powder. The alloy powder contains 49.5% Ag, 20.0% Cu, 30.0% Sn, and 0.5% Pd. Other formulations are available throughout the world.

Excellent reviews of elemental, inorganic, and organic mercury toxicity are available (3, 11, 15, 16). Amalgams can liberate elemental mercury, Hg^{O},[2] in vapor form. The vapor is rapidly absorbed by the lungs (about 80%) and enters the blood where within 1 min it is transported to and crosses the blood-brain barrier. It also enters other organs. In the brain and other tissues, it is quickly oxidized to mercuric mercury. However, ionic mercury that is produced by oxidation of Hg^{O} physically dissolved in the blood will not pass the blood-brain barrier as readily.

The major interest of this laboratory during the last 11 years has been the study of the therapeutically useful, orally effective, water-soluble dimercapto chelating agents (17–19). Examples of these chelating agents are the sodium salt of 2,3-dimercaptopropane-1-sulfonic acid (DMPS) and 2,3-*meso*-dimercaptosuccinic acid (DMSA) (**Fig. 1**). DMPS was developed in the Soviet Union, where it has been an official drug known as Unithiol or Unitiol since the late 1950s (20). In the United States, it has been used successfully to treat humans intoxicated by mercury vapor (21). DMSA was originally de-

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[2]Abbreviations: Hg^{O}, mercury vapor; DMSA, 2,3-*meso*-dimercaptosuccinic acid; DMPS, 2,3-dimercaptopropane-1-sulfonic acid; AAS, atomic absorption spectrophotometer; FDA, Food and Drug Administration.

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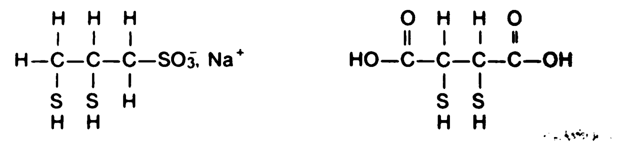


DMPS (2,3-DIMERCAPTO-1-PROPANE-SULFONIC ACID, Na SALT) UNITHIOL, DIMAVAL

DMSA (MESO-DIMERCAPTO SUCCINIC ACID) SUCCIMER

Figure 1. Dimercapto chelating agents.

veloped as sodium dimercaptosuccinate (22) in the People's Republic of China. Both compounds have been used successfully to treat heavy metal poisoning (21, 23–25), including mercury. DMPS as DIMAVAL capsules is approved by the German Food and Drug Administration (FDA), as a mercury antidote and DMPS preparations for parenteral use are available in Germany; DMSA, as Chemet, is approved by the U.S. FDA for the treatment of childhood lead intoxication. A number of reviews of these chelating agents are available (17, 18, 26–28). The clinical experience with DMPS and mercury excretion has been summarized recently in an excellent, thorough review by Kemper et al. (27).

Clarkson et al. (4), in a very timely article, stated that "the release of mercury from dental amalgams makes the predominant contribution to human exposure to inorganic mercury including mercury vapor in the general population." Therefore, the objectives of this study were to determine if the greater the total area of amalgam surfaces, the greater the body burden of mercury and whether there is a correlation between mobilizable mercury (as excreted in the urine after DMPS administration) and the surface areas of dental amalgams in the mouth. In this paper, evidence will be presented that there is a positive linear relationship, with a highly significant coefficient of correlation, between the mercury excreted in the urine after the administration of 300 mg DMPS by mouth and the amalgam score. Also, it appears that two-thirds of the mercury excreted by the group with dental amalgams was derived from dental amalgam mercury.

MATERIALS AND METHODS

Subjects

Fourteen, normal, healthy male and five female undergraduates and graduate students between 18 and 29 years of age were recruited from the University of Arizona campus. In addition, one male research associate, age 49 years, was a subject. Informed written consent was obtained. The experimental protocol was approved by the Human Subjects Committee of this institution. During the week before administration of the chelating agent, a dentist examined each subject and gave him or her an amalgam score. The amalgam score was calculated as follows: A tooth was considered to be a five-sided cube (the sixth side is invisible under the gums). If an amalgam surface had a diameter of 1 mm or less it was given a score of 1; a diameter above 1 and less than 2 mm, a score of 2; and a diameter of 3 mm or more a score of 3. Such a score was given to each amalgam surface on a tooth. The amalgam score is a summation of the score of all the amalgam surfaces on all the teeth in the subjects mouth. A large enough group was initially recruited to allow 10 subjects with no amalgams and 10 subjects with amalgams to make up the study group. Although it was planned to include an equal number of men and women, the number of women volunteers was not sufficient to accomplish this.

Clinical

History, physical exam, removal of blood for analyses by the Clinical Laboratory, and urine pregnancy tests were performed at the beginning of the experiment. Vital signs were monitored during the experiment. Blood was again removed and sent for clinical laboratory analyses at the end of the 9-h period.

Protocol

The subjects were asked not to consume seafood for 30 days before administration of the chelating agent. They were fasted for 11 h before DMPS and 4 h after DMPS administration. Urine was collected at -11 to 0 h and at 1, 2, 4, and 9 h after administration of the chelating agent. The dose of 300 mg DMPS was chosen on the basis of previous clinical reports (27). This dose was given to each subject independent of the body weight because the regimen was being developed as a diagnostic test. Urine was collected in acid-washed graduated cylinders having ground glass stoppers. To the urine immediately after collection, HCl was added, giving a final concentration of 1%. All glassware was washed with 2% nitric acid. All urine samples were processed in duplicate, at least.

Analytical procedures

Urinary mercury was determined by cold vapor generation using an Atomic Vapor Accessory (AVA) Thermo Jarrell Ash Corporation, Franklin, Mass., and a Smith-Hieftje Atomic Spectrophotometer (Thermo Jarrell Ash Corporation). All cold vapor reactions were performed at least in triplicate. The atomic absorption spectrophotomer (AAS) was equipped with a type R106UH photomultiplier tube (Hamamatsu Photonics K. K., Japan) and a Visimax mercury bulb tube (Thermo Jarrell Ash Corporation). The AAS was operated in the single beam mode without background correction at 253.7 nm. Signal quantitation was accomplished by peak height integration during 4-s periods. The AVA cycle was a 30-s argon flush, during which the AAS was autozeroed until a stable reading was obtained. The reaction consisted of adding 7.0 ml 5% $SnCl_2$ (dissolved in 25% HCl) to 25 ml of the acid digested urine, allowing the reaction to proceed for 1 min and purging the vapor for 10 s. A mercury standard curve using cold vapor generation was obtained for 0–240 ng Hg using mercury nitrate (Johnson Matthey Electronics, Ward Hill, Mass.) dissolved in 0.5N HCl and diluted in 3.0 N nitric acid. Total urinary Hg was measured as follows: to aliquots (50 ml) of the acidified urine, 20 ml of concentrated nitric acid was added. The samples were digested at 80°C in a water bath for 14 h. The digested urine was brought to a volume of approximately 100 ml by adding 0.1 N HCl, and kept at room temperature for 24 h. The volumes were adjusted to 100.0 ml by the addition of 0.1 N HCl. The urine samples to be examined for mercury content were processed immediately after collection.

RESULTS

Clinical

All subjects, except one, had an increase in serum iron level at the 9-h period when compared to baseline. In 11 subjects

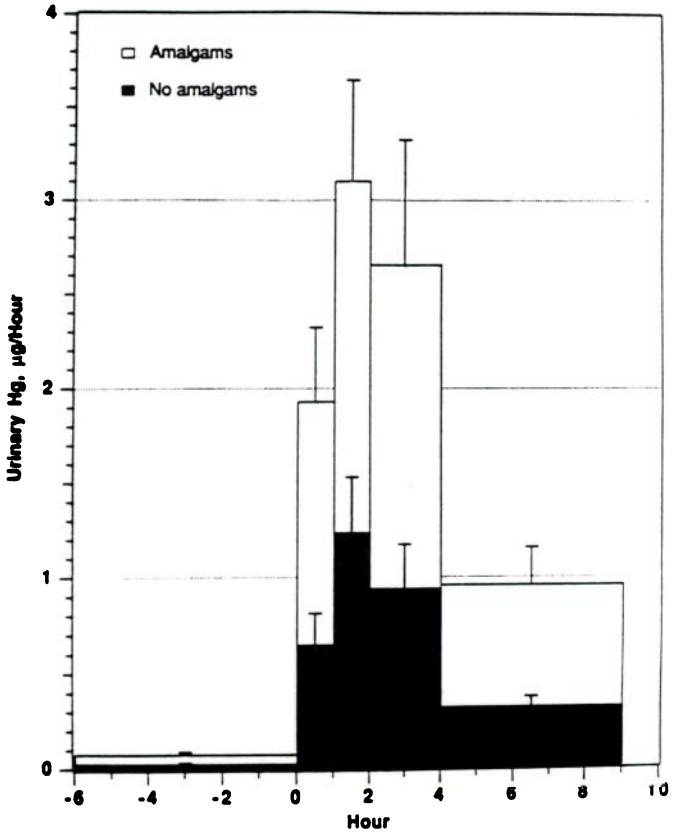


Figure 2. Urinary Hg before and after administration of 300 mg DMPS to volunteers with and without dental amalgams.

the serum iron at the 9-h time point was above the normal range (50–150 µcg/dl) for our clinical laboratory. No other significant drug-related changes from baseline values developed. Two subjects developed nausea within 2 h of drug administration and one of them vomited. One subject developed a macular erythematous rash 1 wk after drug administration. There was no associated fever, constitutional symptoms, or laboratory abnormalities and the rash resolved spontaneously after 2 days. All three subjects developing side effects were female. All other subjects remained asyptomatic. Nausea and rashes have also been reported after administering DMSA (CHEMET, package insert), a similar chelating agent.

Analytical validation

Validation of the analytical method for determing total urinary mercury was performed as follows. To a freshly voided urine of a normal individual, sufficient mercury nitrate was added to achieve final concentrations of 0.50, 5.0, or 30.0 ng/ml. Two aliquots from each spiked urine sample were put through the digestion procedure and analyzed according to the standardized protocol. After correcting for the mercury content of the urine before the spike was added, six determinations of the 30.0 ng Hg/ml gave a mean of 28.2 ng Hg/ml (27.2–29.1 ng/ml), six of the 5.0 ng Hg/ml gave a mean of 4.6 ng Hg/ml (4.5–4.7 ng/ml), and six of the 0.5 ng Hg/ml gave a mean of 0.40 ng Hg/ml (0.35–0.46 ng/ml). The major limitation in the analyses of samples at the 0.5 ng/ml level was the small absorption readings obtained on the spectrophotometer.

DMPS administration increased the urinary excretion of mercury in normal humans

Even before administration of the chelating agent (-9 to 0 h), the 10 normal volunteers with amalgam fillings in their mouths excreted almost threefold more mercury in their urine than did the group with no amalgams, $P < 0.002$ (**Fig. 2, Table 1**). After DMPS administration to individuals of the group with no amalgams, the mean urinary excretion of mercury increased 19-fold. For the amalgam group, it was 25-fold greater after DMPS administration. In individual cases, increases as much as 70-fold and as little as 12-fold after DMPS administration were noted at various collection times. By 9 h after DMPS administration, urinary excretion of mercury by the amalgam filling group was 3.4-fold greater than that of the group without amalgam fillings (Table 1, Fig. 2).

Amalgam score and urinary mercury excretion after DMPS

Linear regression analysis of the mercury excreted after DMPS administration indicated a highly significant positive linear correlation with the amalgam score (**Fig. 3**). Two hours after DMPS administration there was a definite positive linear relationship ($r = 0.95$) between amalgam score and the urinary mercury after DMPS administration. The correlation coefficients for 1, 4, or 9 h after DMPS administration (Fig. 3) decreased with time at the 0- to 4-h and 0- to 9-h periods but they were still highly significant.

DISCUSSION

The results of the present experiments show that there is a pool of inorganic mercury in the human body that can be mobilized by administering the chelating agent DMPS and that more mercury is excreted by individuals with amalgams than those without (Table 1 and Fig. 2). A linear relationship exists between the amalgam score and the urinary mercury after DMPS administration (Fig. 3). Those subjects with amalgams had an average urinary mercury excretion before and after DMPS administration of approximately threefold more than that found for those without amalgams (Table 1 and Fig. 2). Therefore, it appears that two-thirds of the Hg in the urine of students with amalgams originated from mercury vapor that initially had been released from the amalgams in their mouths. The mercury vapor (Hg^O) in the blood and in the brain was then oxidized to mercuric Hg, which was then stored in the tissues. A great deal of the mercuric Hg was deposited finally in the kidneys. It is mercuric Hg that is chelated and excreted in the urine after DMPS treatment, not the Hg^O form. Chelation chemistry theory

TABLE 1. *Urinary mercury excretion before and after the oral administration of 300 mg DMPS to normal individuals with and without dental mercury amalgams*[a]

	No amalgam	Amalgam	*P*
-9–0 h	0.27 ± 0.04	0.70 ± 0.11	<0.002
0–9 h	5.10 ± 1.11	17.16 ± 3.32	<0.003
P	<0.001	<0.001	

[a] Values are given as µg Hg ± SE. $N = 10$ for each group. DMPS was given at time zero.

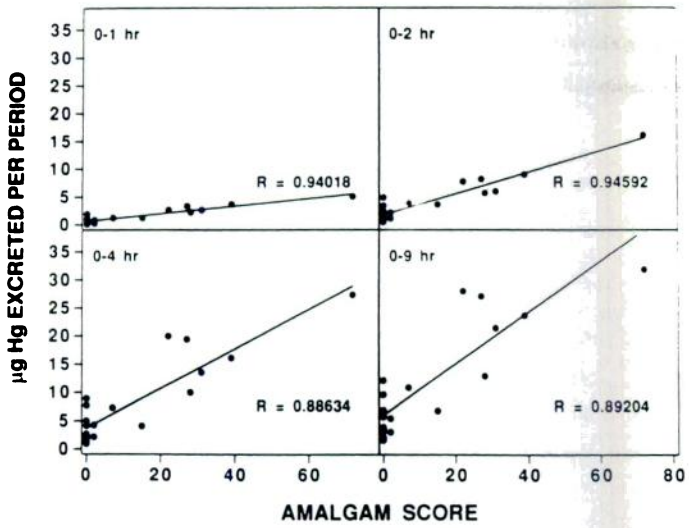


Figure 3. Amalgam score vs. urinary Hg excretion after DMPS administration. The mercury excretion after DMPS administration has been corrected by subtracting the mercury excretion found for the same length of time before administering DMPS. This was done by collecting the urine for 11 h before DMPS administration and determining the mercury content per 11 h and then calculating the mercury excretion per hour. R = coefficient of correlation.

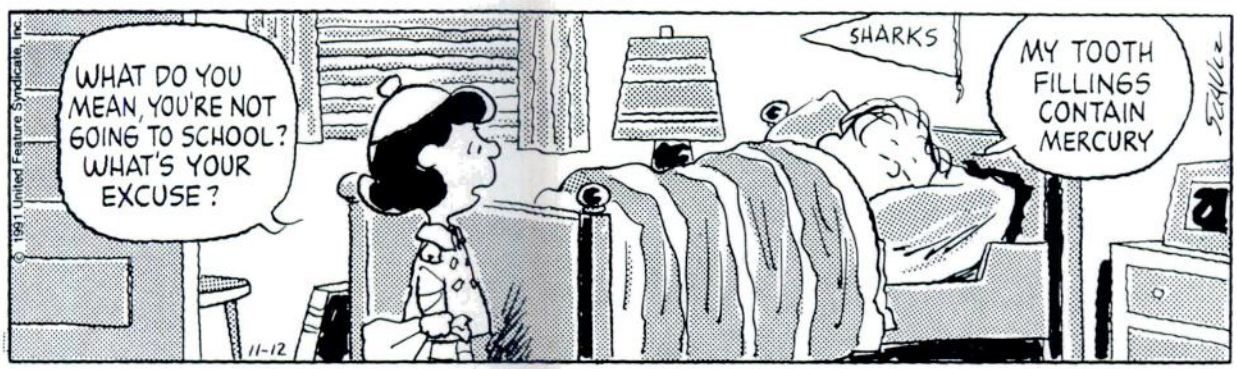
indicates that DMPS chelates mercuric Hg, not elemental Hg.

Some investigators have not found a correlation between urinary mercury levels and amalgams (29); others have (30–32), but the correlations were limited (e.g., $r=0.54$) because of different experimental standards and approach. In addition, the amounts of mercury found in the urine were usually small and near the detection limits of the methods used. We have clearly established that DMPS will mobilize more mercury in individuals with dental amalgams than those without. At the present time, however, there is no unequivocal evidence that such amounts of mercury in the human body are harmful to the individual's health. Of course this excludes the rare individuals who are hypersensitive to mercury. Our experimental results cannot be used to support either side of the controversy dealing with whether the amount of mercury vapor liberated from dental amalgam is harmful or involved in the etiology of disease (or diseases) (1, 2, 9, 10). In sufficient amounts there is no question that mercury can be toxic. Clarkson (33) in a provocative article has called mercury "the element of mystery." Certainly as far as dental amalgams are concerned, the mystery as to the degree of toxicity and whether this causes clear systemic effects or symptoms in the most sensitive groups in the general population will continue until more sensitive biological markers of mercury exposure can be developed.

One problem in interpreting the significance of many publications dealing with mercury from dental amalgams has been the absence of validation of the methods used to quantitate mercury. The problems involved in determining mercury content of urine are many, including adsorption of mercury to the walls of containers, questionable analytical procedures and techniques, as well as the importance of beginning the analytical procedure as soon as the urine is collected. As Clarkson et al. (4) have stated about mercury analysis used in studies of the amalgam question, there is ". . . uncertainty about analytical quality control. . . . Details on analytical quality control are missing." In the present paper, validation data are presented and were found to be acceptable.

One should not overlook the other important results of the present studies. It appears that DMPS warrants further investigation as a means of measuring in humans the kidney burden of and perhaps the body load of mercury and other heavy metals and metalloids such as lead and arsenic. Cherian et al. (34) indicated the feasibility of doing this for mercury using experimental animals. Molin et al. (35), however, have indicated that in humans the mercury mobilizable after a single DMPS dose is mainly an index of recent exposure and is not affected by slow body pools or long-term exposure. Unfortunately, a precise definition of recent exposure was not included in their publication. The data of Roels et al. (36) suggest that the urinary mercury before and after DMSA administration ". . . mainly reflects the amount of mercury stored in the kidney. . . ." Buchet and Lauwerys (37) found that either DMPS or DMSA mobilizes mercury stored in the kidney and can be used to determine the renal burden of mercury. The rate of removal of mercury, however, was greater with DMPS than with DMSA.

DMPS might be expected to increase the ease of measuring biological exposures to other toxic heavy metals and metalloids as its administration increases the urinary excretion of many of them (21, 26, 27). Highly toxic metals and metalloids have many uses in an expanding high-tech society, e.g., the use of arsine and gallium arsenide in the semiconductor industry (38). Unlike the $CaNa_2EDTA$ challenge or mobilization test that has been used in medicine and is now suspect as to its safety (39), DMPS does not cause a redistribution of Hg to the brain or other organs of the body (40), and it is more specific than $CaNa_2EDTA$ in that at diagnostic doses it would not be expected to increase the urinary excretion of essential metals such as copper and zinc (25) at clinically important levels. FJ



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