Mercury Excretion and Intravenous Ascorbic Acid

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ABSTRACT. We tested the hypothesis that intravenous ascorbic acid increases urinary excretion of mercury in subjects with low mercury levels from dental amalgam, food, and other sources. From 89 adult volunteers we selected 28 subjects with the highest mercury excretions (2 to 14 μg/24 h). We administered intravenous infusions of 500 ml lactated Ringer's solution with and without addition of 750 mg of ascorbic acid/kg body weight, up to 60 g ascorbic acid. Average mercury excretion during the 24 h after infusion of ascorbic acid was 4.0 ± 0.5 μg (mean ± *SEM*), which was not significantly more than after infusion of Ringer's solution alone (3.7 ± 0.5 μg). Lead excretion was similarly unaffected. If ascorbic acid administered intravenously benefits some persons with suspected adverse reactions to mercury, the benefit in subjects similar to ours appears unrelated to short-term enhanced excretion of mercury or lead.

A RELATIONSHIP between mercury toxicity and ascorbic acid was suggested as early as 1840.[1] Early research with dogs found that intravenous (IV) ascorbic acid lessened the acute toxicity of one of three tested mercury-containing diuretics.[2] More recent animal studies have shown similar partial benefits. Hill concluded that dietary ascorbic acid reduces the chronic toxicity of oral mercuric chloride ($HgCl_2$) in chicks.[3] Carroll et al. reported that ascorbate injected in rats prior to an acute dose of $HgCl_2$ strikingly reduced kidney damage, intestinal lesions, and mortality.[4] Nevertheless, Blackstone et al.[5] and Murray and Hughes[6] found that a large oral intake of ascorbic acid increased deposits of mercury in guinea pig liver, kidney, and brain from oral $HgCl_2$. In rats, oral ascorbic acid counteracted some effects of oral $HgCl_2$ but failed to prevent growth retardation.[7] The possible human implications of these studies are unclear for many reasons, including the internal synthesis of large amounts of ascorbate in chicks and rats but not in guinea pigs or humans. In humans, Calabrese et al. found no significant effect of 500 and 1 000 mg/d of oral ascorbic acid on mercury in hair (1 mmole = 176 mg).[8]

There appear to be no published human studies of mercury in relation to IV ascorbate. Nevertheless, an estimated 500 or more dentists have attended professionally sponsored meetings about the use of IV ascorbate for mercury toxicity, and many use it in their practice. They believe the use of IV ascorbate during removal of mercury amalgam restorations is beneficial. This practice is based on limited clinical impressions and plausible hypotheses presented by Queen,[9] but it has not been studied scientifically.

One way that IV ascorbate might function is to increase mercury excretion.[9] Given our experience with IV ascorbic acid and mercury analysis, we were asked by a private foundation to study the effect of IV ascorbic acid on mercury excretion. Ascorbate might increase excretion through its ability to weakly chelate heavy met-

als,[10] or its strong ability to reduce inorganic mercury ions to the elemental form in vitro[11] might facilitate mobilization of protein-bound mercury that could then be excreted.

In an attempt to test these possibilities, we measured urine mercury excretion after infusion of lactated Ringer's solution, with and without addition of a large dose of ascorbic acid (as sodium ascorbate). For comparison, we also measured lead in the same samples. We used mostly local volunteers with the highest mercury excretions we could find. These excretions were much less than is generally considered toxic (> 50 to 100 μg/24 h; 1 μmole = 201 μg), but they seem typical of dental patients being treated with ascorbic acid.[9]

Materials and methods

We sought volunteers through the local news media, word-of-mouth advertising, and from subjects tested previously by our laboratory for mercury excretion. Interested persons were sent information on the study and three questionnaires about their medical and dental histories, mercury exposure, and symptoms that might relate to chronic mercury toxicity. The mercury exposure questionnaire asked about potential exposure from 55 occupations or hobbies, plus 8 other sources including drugs, cosmetics, and consumption of three or more servings per week of specified fish species (form adapted from Queen[12]). On the symptom questionnaire, subjects rated 55 potential mercury-related symptoms[12] in four degrees, ranging from *never* to *always/severe*.

Of 93 volunteers who returned completed questionnaires, 89 signed a consent form and gave a 24-h urine sample for screening of their mercury excretion (most attended small-group meetings at our facility). The consent form and protocol were approved by our institutional review board. The 24-h urine collection procedure was explained to each subject and was repeated on a label attached to the urine collection bottles (4–1 polyethylene, Fisher Scientific). Subjects recorded the beginning and ending collection times on the label. Four volunteers dropped out; 2 because of their physicians' concern about interference with newly prescribed drugs, 1 because of inadequate bladder control as a result of multiple sclerosis, and 1 because of scheduling conflicts. We excluded 1 subject who decided to have amalgam fillings removed during the study. These changes resulted in 84 potential subjects .

Control infusion and blood test. Those potential subjects who showed at least 2 μg mercury/24 h in the urine screening (32 of 84) were asked to return about 3 wk later in the morning to give fasting blood and urine samples for standard screening tests and to receive a control IV infusion.

The infusion, which lasted about 2 h, contained 500 ml of lactated Ringer's solution (Kendall McGaw Labs, Irvine, CA), 120 ml of injectable saline solution (0.9%), and 25 mg EDTA (0.8 mmole). We included this small amount of EDTA because the later IV ascorbic acid infusion included a similar amount as preservative. This precaution seems largely symbolic because we have found that even 3 g of IV EDTA does not affect mercury excretion.[13] The second 24-h urine sample was collected beginning at the time of initiation of the Ringer's infusion and was analyzed for mercury and lead. The screening tests excluded one person with excessive blood urea nitrogen (> 30 mg/dl = 1.06 mmole/l) and serum creatinine (> 1.7 mg/dl = 150 μmole/l). Three subjects were dropped at this point because they lived more than 500 miles (804.5 km) away, thus leaving 28 subjects.

Test infusion. The 28 subjects were asked to return in the morning about 3 wk later. They were given an IV infusion of 500 ml lactated Ringer's solution with approximately 80 to 120 ml of ascorbic acid solution (Ascorbic Acid Injection, 500 mg/ml, pH 5.8 to 6.3, with 0.25 mg EDTA/ml; Steris Laboratories, Phoenix, AZ). The dose was 750 mg/kg for body weights up to 80 kg (60 g ascorbic acid), and 60 g for body weights greater than 80 kg. As was done before, 24-h mercury and lead excretions were measured. Given that mercury excretion reportedly shows a weak diurnal variation detectable in large groups,[14] the control and IV ascorbic acid infusions were all done at the same time of day to avoid any possible variability from this cause.

Mercury and lead analyses. Mercury was analyzed with a Perkin-Elmer MAS-50A mercury analyzer, based on the method of Hatch and Ott.[15] Lead analyses used a Perkin-Elmer HGA-500 graphite furnace and model 306 atomic absorption spectrophotometer with deuterium background correction lamp. Mercury analyses of split samples by our lab and in comparison with two other labs (National Medical Services, Inc., Willow Grove, PA, and Huggins Diagnostic Center, Colorado Springs, CO) indicate that our analytical variability was approximately ± 2 μg/24 h for samples containing 0–10 μg/24 h. This variability is generally less than the daily and weekly biological variability within our subjects. Biological variability of twofold or more is also common in persons excreting far higher amounts (100 to 1 000 μg/d).[16-18]

Breath and stool excretion. We explored possible enhanced excretion in breath and feces using two subjects with urinary excretions of 6 μg and 4 μg/24 h, respectively. Stools were collected and weighed during the 2 d before and 3 d after IV ascorbic acid infusion. Samples were transferred to plastic vials supplied with the Protocult stool collection kit (ABC Medical Enterprises, Rochester, MN). They were stored frozen until all were sent together for mercury analysis by National Medical Services.

Breath samples from the same two subjects were analyzed before, during, and after the IV ascorbic acid infusion by a Jerome Model 411 mercury vapor analyzer (Arizona Instrument Corp., Tempe, AZ). Subjects inhaled a deep breath through their nose only (to avoid mercury immediately attributable to their amalgam fillings); they then held their breath for 20 s, following which they exhaled their breath through their nose into a plastic face mask connected to a plastic bag. Samples of 125 ml (10 s) were quickly taken by the analyzer probe located in the center of the bag (beyond possible diffusion contact with the plastic bag in this brief time). This system showed expected responses to two sources of mercury vapor: (1) orally exhaled air following chewing gum

with molar teeth containing amalgam restorations, and (2) calibration tests with measured volumes of saturated mercury vapor as described by the instrument manufacturer.

Statistical analyses were performed with Systat software (version 4.2, Systat, Inc., Evanston, IL).

Results

In Table 1 are shown characteristics of the 89 subjects screened and used for correlation studies.

Average urinary mercury excretion (± *SEM*) was 4.0 ± 0.5 μg in the 24 h after IV ascorbate infusion (range = 0–12 μg/24 h) versus 3.7 ± 0.5 μg/24 h after the control infusion (range = 0–10 μg/24 h). This slight increase was not statistically significant by paired *t* test ($p = .30$, one-tailed, $n = 28$).

The biological and analytical variability necessitated including more than a few subjects for this finding. Six subjects showed apparent *increases* of 3 μg/24 h or more after the IV ascorbic acid infusion, compared with the control infusion. However, these are balanced by five subjects who showed apparent *decreases* of 3 μg/24 h or more after IV ascorbic acid infusion. These results serve as a caution against trying to establish the effects of IV ascorbic acid from too few determinations.

Whether oral vitamin C supplements taken by most subjects might have affected our conclusions was determined by analyzing the 5 subjects who reported no supplementation and the 3 subjects who reported taking supplements of 100 mg/d or less. Their average mercury excretions after IV ascorbate infusion were *less* than was found after the control infusion. These differences (1 and 1.5 μg, respectively) are not statistically significant ($p \geq .20$) or well defined with so few subjects; however, the differences provide argument against the possibility that the supplements taken by 23 of our subjects (average 2.9 g/d) might have blunted the effect of IV ascorbate. In any case, oral supplements of 3 to 5 g/d are recommended[12] for patients planning to undergo amalgam removal with IV ascorbate; therefore, our subjects resemble these patients regarding oral supplement.

Like mercury, the average urinary excretion of lead was not significantly increased by IV ascorbic acid infusion (24 ± 3 μg/24 h versus 21 ± 2 μg/24 h after the control infusion; $p = .20$, one-tailed, $n = 28$; 1 μmole = 207 μg).

We did not randomize the order of control and test infusions because that would have added an additional subject visit and delay, with no known benefit. The two infusions were separated by about 3 wk, which is far longer than the retention of a large dose of ascorbate.

We found no evidence for enhanced excretion of mercury in breath or stools of two subjects, within the marginal limits of our ability to detect the low levels found. During the 3 d following ascorbic acid infusion, stool mercury averaged roughly 25 μg/d in both subjects—no more than during the previous 2 d. Breath samples usually showed 0 μg Hg/l before infusion, with a few irreproducible readings of 2 to 10 μg/l. Measurements at three times during the 2-h infusions and three times up to 4 h afterwards showed the same pattern, with 28 of 39 samples showing readings of 0 μg/l and 32 of 39 samples showing readings of <2 μg/l. Levels during gum chewing were elevated consistently (7–25 μg/l). These exploratory measurements found no large increased excretion in stools or breath, but detection of small increases would require further research.

We analyzed our data for possible correlations between mercury excretion, mercury exposure, symptoms that might relate to mercury, and laboratory data. Bearing in mind that 5% of raw correlation coefficients are expected to be spuriously "significant" at the .05 level, we report the following observations.

There was a weak positive correlation between initial excretions of mercury and lead (rank correlation = 0.33, $p < .05$, $n = 28$). This might reflect common sources of mercury and lead, or common factors favoring absorption or retention.

In the screened group of 89, there were no statistically significant correlations between urinary excretion and various measures of exposure from amalgam fillings (number of fillings, fillings × duration, etc.). Nor was mercury excretion detectably correlated with 63 measures of other potential exposure, including occupational, environmental, pharmaceutical, or dietary (fish) exposure. Similarly, among 55 correlation coefficients of urinary mercury with symptoms that might relate to mercury, none was positive and individually statistically significant at the $p = .05$ level. There was a weak and understandable correlation of excretion with body weight ($r = 0.24$, individual $p = .02$).

Table 1.—Characteristics of Screened Subjects*

Characteristics	$\bar{X}$	Range (*SD*)
Age (y)	51	11 to 73 (12.9)
Weight (kg)	68	30 to 121 (14)
No. current amalgam fillings	9	0 to 30 (6.1)
Mean age of amalgam fillings (y)	20	0 to 55 (13.0)
No. fillings replaced by crowns and dentures	5	0 to 65 (8.8)
Mean age of crowns and dentures (y)	10	0 to 54 (11.4)
Supplemental oral vitamin C in the 68 subjects who used it (mg/d)†	2 400	30 to 11 000 (2450)

*Screened subjects numbered 89: 26 men and 63 women.
†1 mmole = 176 mg.

Discussion

The relatively low urinary mercury excretions of our generally nonoccupationally exposed (0–10 μg/d) subjects were not increased by a large dose of IV ascorbic acid. If typical adult body burdens of mercury are of the order of 13 000 μg,[19] then its practical removal by IV ascorbate infusion would require that each infusion increase excretion by at least the order of 100 μg. This clearly did not occur in our subjects. Whether other subjects with much higher levels might excrete more mercury with IV ascorbate remains unknown.

Our findings do not preclude the possibility that ascorbic acid might have beneficial effects by mecha-

nisms other than enhanced excretion of mercury. For example, addition of 1% ascorbic acid to the diet of Japanese quail prevented the mortality, weight loss, and anemia otherwise caused by cadmium (75 mg/kg diet = 0.67 mmole/kg). However, the ascorbic acid did not reduce tissue levels of cadmium[20]; apparently it acted internally to reduce the toxic activity of cadmium. If such effects of oral or IV ascorbic acid on mercury occur in humans, they remain to be demonstrated.

Drugs used to treat mercury toxicity include *N*-acetyl-d,l-penicillamine,[17] penicillamine,[18] and dimercaptosuccinic acid (DMSA).[21] These drugs generally increase urinary excretion of mercury two- to fourfold, with most excretion occurring within the first 8 h of DMSA administration. Intravenous ascorbate clearly had no comparable effect in our subjects. Unfortunately, the potential toxicity of these drugs limits the circumstances and duration of their use.

The lack of detectable correlation in our subjects between a single measurement of urinary mercury excretion and various measures of exposure or potential symptoms is perhaps not unexpected with our number of subjects (i.e., 89). Previously reported correlations of this type are weak and may require hundreds of subjects and repeated measures of excretion and exposure.[22]

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