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A dose-dependent relationship between mercury exposure from dental amalgams and urinary mercury levels: a further assessment of the Casa Pia Children's Dental Amalgam Trial

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Abstract

Dental amalgams are a commonly used dental restorative material, and amalgams are about 50% mercury (Hg). In our study, urinary Hg levels was examined in children of age 8–18 years, with and without dental amalgam fillings, from a completed clinical trial (parent study) that was designed to evaluate the potential health consequences of prolonged exposure to Hg from dental amalgam fillings. Our study was designed to determine whether there was a significant dose-dependent correlation between increasing Hg exposure from dental amalgams and urinary Hg levels. Hg exposure depends on the size and number of teeth with dental amalgams. Overall, consistent with the results observed in the parent study, there was a statistically significant dose-dependent correlation between cumulative exposure to Hg from dental amalgams and urinary Hg levels, after covariate adjustment. Further, it was observed that urinary Hg levels increased by 18% to 52% among 8 to 18 year old individuals, respectively, with an average exposure to amalgams, in comparison to study subjects with no exposure to amalgams. The results of our study suggest that dental amalgams contribute to ongoing Hg exposure in a dose-dependent fashion.

Keywords

dose dependent; mercury; toxicokinetics; urine

Introduction

Dental amalgams are a commonly used dental restorative material. Amalgams are sometimes referred to as 'silver fillings' because of the silver color and its use as a 'filling' for dental cavities; however, amalgams are about 50% mercury (Hg) and the remainder is made up of silver and some tin, copper, and zinc. According to the US Food and Drug Administration (FDA), dental amalgams release '... low levels of Hg vapor, with higher amounts released with mastication and gum chewing. Higher levels of exposure to elemental mercury vapor are also associated with placement and removal of dental amalgams.' Because Hg is a known neurotoxin, amalgams are banned in some countries.[1]

To date, the issue of safety in the use of amalgams is still being debated, with conflicting research findings.[2-6] In 2009, the FDA concluded that dental amalgam is a safe and effective restorative treatment; however, after receiving several petitions raising concerns on specific issues, the FDA reviewed the use of amalgams in late 2010. One of the issues of concern

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raised was '... the exposure of pediatric populations to Hg vapor.'[7]

In our study, urinary Hg levels was examined in children of age 8–18 years, with and without dental amalgam fillings, from a completed clinical trial (the parent study) that was designed to evaluate the potential health consequences of prolonged exposure to Hg from dental amalgam fillings.[8-10] Our study was designed to determine whether there was a significant dose-dependent correlation between increasing Hg exposure from dental amalgams and urinary Hg levels.

Methods

The original study protocol from the parent study was approved by the institutional review boards at the University of Washington and the University of Lisbon. All parents or guardians gave written consent, and all children provided signed assent. Principal design and analytical issues involved in this trial as well as principal outcome measures have been reported.[8-10] Our study was undertaken by reanalyzing data sets provided to us by the investigators involved with the parent study.

Study population

The cohort of children examined in our study came from the Casa Pia clinical trial on the health effects of dental amalgam fillings in children.[8-10] As described previously, the children examined were residents of the Casa Pia school system in Lisbon, Portugal, and were 8–12 years old at the study inception.[8-10] Eligibility requirements excluded children with preexisting neurological or developmental disabilities. Subjects were initially randomized to Hg amalgam (treatment) or composite resin (control) dental care groups. Children were evaluated at baseline and at seven subsequent annual intervals after the initial dental treatment. An extensive battery of neurobehavioral, neurological, renal function, urinary Hg, and urinary porphyrin assessments were used in each evaluation. In addition, detailed information was collected from each child's mouth regarding the composition, number, size, and positioning of dental fillings. Table 1 summarizes the baseline measurements recorded on the cohort of children ($n = 462$) examined in our study. In our analyses, we did not modify the original data set provided to us from the parent study.

Table 1. A summary of the baseline measurements for all subjects (n = 462) examined in our study

Baseline measurements	
Mean age ± SD (yrs)	10.11 ± 0.9
Gender (% male)	57
Asian (%)	1
Black (%)	29
White (%)	70
Mean blood lead level ± SD (μg/dL)	4.63 ± 2.4
Urinary mercury level ± SD (μg/L)	1.48 ± 1.1
Uroporphyrin (μg/L)	8.56 ± 8.8
Heptacarboxyporphyrin (μg/L)	1.76 ± 2.8
Hexacarboxyporphyrin (μg/L)	0.43 ± 0.8
Pentacarboxyporphyrin (μg/L)	1.35 ± 3.1
Precoproporphyrin (μg/L)	3.56 ± 3.9
Coproporphyrin (μg/L)	34.84 ± 38.4

Urine sample collection procedures

As previously described, a urine sample (~50 mL) was collected from each child at baseline and at each subsequently scheduled annual visit to the University of Lisbon School of Dental Medicine for dental, neurological, and neurobehavioral evaluations. Immediately following urine collection, a 10-mL aliquot was removed and was acidified with 1 N hydrochloric acid (HCl) for use in Hg analysis by continuous-flow, cold-vapor spectrofluorometry. Urinary Hg levels were calculated as micrograms per liter of urine.[10] It was not possible to correct for dilution by normalizing with urinary creatinine levels because this information was not provided to us by the investigators involved with the parent study.

Estimating the Hg exposure variable

The number of amalgam restorations of the buccal, distal, lingual, and occlusal surfaces (no amalgam restorations were recorded for medial or incisal surfaces) was counted and the level of exposure was computed by applying scores of 1.0, 2.0, or 3.0 for small, medium, or large restorations, respectively, then adding these scores to each restoration of each tooth for each year. Other weighting schemes for large, medium, and small sizes were also considered (i.e. 1.0, 4.0, 9.0; 1.0, 8.0, 27; 1.0, 1.0, 1.0; and ln(1.0), ln(2.0), ln(3.0)). However, the weighting scheme that best correlated with urinary Hg levels (using only amalgam subjects who were 12 years or older to avoid any issues with baby teeth) was 1.0, 2.0, and 3.0. Thus, this weighting scheme was used to create the yearly exposure scores used in all of our

subsequent analyses. In addition, since baby teeth (which comprised 22% of restorations) are smaller than adult teeth, the exposure for baby teeth was taken to be one half the exposure for adult teeth (i.e. with scaling factors of 0.5, 1.0, and 1.5 for small, medium, and large restorations, respectively). Further, as the subject weights were not available, each yearly exposure score was divided by the subject's estimated body mass index (BMI) based on the subject's age and gender. The estimated BMI scores for age and gender utilized in our study were obtained from the Centers for Disease Control and Prevention's (CDC) BMI 50th percentile clinical growth charts (http://www.cdc.gov/growthcharts/clinical_charts.htm#Summary). The BMI-normalized yearly exposure scores were accumulated from year to year. Thus, a restoration contributed to exposure for the year it was placed and each subsequent year, unless a tooth had been lost in a given year, in which case its exposure contribution was set to zero for that year and all subsequent years. This procedure was applied to both baby teeth and adult teeth.

The exposure score for each year was assumed to affect the outcome measure for the same year. The assumption that exposure in a year affected outcomes in the next year was also considered. However, the first assumption produced a better fitting model.

Table 2. A summary of mean mercury exposure from dental amalgams[a] by the age of study subjects[b]

Study subject's age (yrs)	Study subject's dental amalgam mean exposure
8	10.8
9	11.0
10	10.8
11	11.7
12	12.5
13	14.2
14	15.2
15	16.7
16	19.0
17	19.8
18	19.9

[a]Exposure was measured by counting the number of restorations using amalgam, then an exposure score was computed by first giving scores of 1, 2, or 3 for small, medium, or large restorations, respectively, then adding these scores for each restoration of each tooth. Exposure for baby teeth was taken to be one half the exposure for adult teeth (i.e. ½, 1, 1½ for small, medium, and large restorations). Each exposure score was divided by the subject's theoretical BMI determined by the subject's age and gender. The exposure scores for each restoration done in a year were added together to form the BMI-normalized score for that year and the scores were accumulated from year to year. If a tooth no longer existed at a given year, the exposure was set to zero for that year and all subsequent years. This procedure was applied both to baby teeth and adult teeth.

[b] Includes only subjects assigned to the dental amalgam group.

Statistical analyses

In all our statistical analyses, a two-tailed p value of <0.05 was considered statistically significant.

Both amalgam and composite groups were included in the analysis, but all participants in the composite group had an amalgam exposure level of zero except for two subjects who received amalgam restorations in error. Since repeated measures were collected for each subject, a mixed-effects repeated-measures model was used to estimate the relationship between exposure and urinary Hg level. This type of model takes account of the correlation between repeated observations of the same subject and allows for the inclusion of subjects with missing data. The model included terms for subject, age as the repeated measurement factor, exposure, and the following covariates: gender, race, baseline level (i.e. study year 1) of urinary Hg, baseline urinary porphyrin measures (uroporphyrin, heptacarboxyporphyrin, hexacarboxyporphyrin, pentacarboxyporphyrin, precopropophyrin, and coproporphyrin), and the baseline level of lead (Pb) in each subject's blood. Interaction terms were added if they contributed significantly to the model. Ordinarily, one would use study year as the repeated factor because it measures time from the beginning of the intervention. Since the present analysis is not comparing intervention groups however, it is more reasonable to use age as the repeated factor. A log transformation of Hg level was used to satisfy the normality requirement for the statistical procedure. This model can be specified as follows:

$$y_{ia} = b_0 + b_1 E_{ia} + b_2 a + b_3 c_{i1} + \ldots + b_{13} c_{i11} + v_i + u_{ia}$$

where y_{ia} is the log of Hg level for the ith subject at age a, E_{ia} is the amalgam exposure level for the ith subject at age a, c_{i1}–c_{i11} represent the 11 covariates described above for the ith subject, v_i and u_{ia} are subject and age random effects. The coefficient b_1 represents the effect of amalgam exposure level on Hg level. Table 2 summarizes the mean Hg exposure from dental amalgams by the age of the study subjects.

Table 3. A summary of the relationship between cumulative exposure to mercury from dental amalgams[a] and urinary mercury measurements

Outcome measurement (μg/L)	β-Coefficient[b]	Standard error	Degrees of freedom	*T* statistic	*p* value
Unadjusted urinary mercury	0.017	0.001	540	14.05	<0.0001
Adjusted urinary mercury[b]	0.018	0.001	513	14.48	<0.0001

[a] Exposure was measured by counting the number of restorations using amalgam, then an exposure score was computed by first giving scores of 1.0, 2.0, or 3.0 for small, medium, or large restorations, respectively, then adding these scores for each restoration of each tooth. Exposure for baby teeth was taken to be one half the exposure for adult teeth (i.e. 0.5, 1.0, and 1.5 for small, medium, and large restorations). Each exposure score was divided by the subject's estimated BMI determined by the subject's age and gender. The exposure scores for each restoration done in a year were added together to form the BMI-normalized score for that year and the scores were accumulated from year to year. If a tooth no longer existed at a given year, the exposure was set to zero for that year and all subsequent years. This procedure was applied both to baby teeth and adult teeth.

[b] Each outcome estimate was adjusted for the baseline level (i.e. study year 1) of urinary mercury, each porphyrin measure, gender, race, and blood lead level.

Results

Table 3 summarizes the relationship between the BMI-normalized cumulative exposure to Hg from dental amalgams and urinary Hg levels in the model we constructed. A significant exposure effect means that the urinary Hg level is significantly affected by the level of exposure after adjustment for covariates. A positive estimate implies that higher levels of exposure are associated with higher Hg levels of the outcome measured, while a negative estimate implies that higher levels of exposure are associated with lower Hg levels. Overall, there was a statistically significant correlation between BMI-normalized cumulative exposure to Hg from dental amalgams and urinary Hg levels. The basic trend of the urinary Hg level versus age data revealed that the urinary Hg level was initially higher in the amalgam exposed group, but as the children aged, urinary Hg decreased more rapidly in the composite group. Furthermore, from the model constructed it was observed that baseline level of Pb in each subject's blood (β-coefficient $= -0.033$, standard error $= 0.010$, degrees of freedom $= 426$, T statistic $= -3.35$, p value $= 0.0009$), gender (β-coefficient $= -0.098$, standard error $= 0.028$, degrees of freedom $= 426$, T statistic $= -3.46$, p value $= 0.0006$), baseline age (β-coefficient $= -0.032$, standard error $= 0.005$, degrees of freedom $= 467$, T statistic $= -6.85$, p value < 0.0001), and baseline urinary Hg level (β-coefficient $= 0.079$, standard error $= 0.038$, degrees of freedom $= 427$, T statistic $= 2.10$, p value $= 0.036$) all had statistically significant effects on urinary Hg levels.

As shown in Table 4, it was observed that urinary Hg levels increased by 18% to 52% among 8 to 18 year old individuals, respectively, with an average exposure to amalgams, in comparison to study subjects with no exposure to amalgams.

Table 4. Estimated urinary mercury level by age and level of exposure

Age (yrs)	Urinary mercury level[a] (zero exposure)	Urinary mercury level[a] (ave. exposure)	Δave. exposure vs. zero exposure
8	2.77	3.28	0.51
9	2.68	3.22	0.54
10	2.60	3.17	0.57
11	2.51	3.13	0.62
12	2.43	3.09	0.66
13	2.36	3.06	0.70
14	2.28	3.04	0.76
15	2.21	3.03	0.82
16	2.14	3.03	0.89
17	2.07	3.03	0.96
18	2.00	3.04	1.04

[a] μg Hg/L of urine.

Discussion

The results of our study suggest that extent of excretion of Hg in the urine is related to the exposure from dental amalgams in a dose-dependent fashion. The findings from our study are consistent with previous studies examining Hg exposure from dental amalgams. For example, investigators examined US children over a 5-year period and found that the number of amalgam restorations had a significant dose–response relationship with Hg urine levels.[11] Similarly, other investigators found that the number of amalgam surfaces was related to the emission rate of Hg into the oral cavity and to the excretion rate of Hg by urine.[12] Finally, a

positive correlation was found between urine Hg concentration and extent of amalgam restoration.[13]

A further study found that, in adults, Hg excretion correlated with the number of amalgam fillings.[14] They also found that immediately post removal (up to 6 days after removal), there was a mean increase of 30% and that within 12 months after removal of all amalgam fillings, the participants showed substantially lower urinary Hg levels. Other investigators found, in adult males, a significant correlation between amalgam exposure and both urinary and blood Hg concentrations.[15] They estimated from the data that, on average, each 10-fold increase in amalgam exposure is associated with an increase of 1 μg Hg/L in urine concentration. This observation is consistent with the magnitude of increased urinary Hg levels observed in our study.

It is also noteworthy that our results are consistent with those observed from the parent study.[10] In the parent study it was observed that the urinary Hg concentrations were highly correlated with the number of amalgam fillings when comparing subjects in the dental amalgam group to the composite group.[10] Our study is differentiated from the parent study in that we constructed statistical models to specifically examine the relationship between dose-dependent dental amalgam exposure variables and urinary Hg levels with examination of multiple covariates.

Interestingly, our study revealed several covariates with known biological effects statistically significantly impacting the outcome measurement of urinary Hg levels, including baseline level of Pb in each subject's blood, gender, and baseline age. Among the aforementioned covariates, it was observed that baseline levels of Pb in each subject's blood were significantly inversely related to the urinary Hg levels. Consistent with the observation in our study, previous studies have reported that Pb intoxication may actually accentuate Hg intoxication.[16] In addition, among the covariates examined, it was observed that female study subjects had significantly higher urinary Hg levels than male study subjects. Consistent with the observation in our study, previous studies reported that females excrete significantly higher levels of Hg than males following Hg exposure.[17] Furthermore, among the covariates examined, it was observed that there was a significant inverse relationship between the baseline age of a study participant and urinary Hg levels. Consistent with the observation in our study, previous studies revealed that Hg excretory pathways develop with age, and hence, the younger one is exposed to Hg, the more potential for experiencing Hg-associated adverse effects.[18]

It should be pointed out that urinary Hg excretion is a minor excretory pathway and that about 90% of excretion of inhaled Hg vapor is eliminated in feces.[18] Also, it is well known that Hg is a retained toxicant, with a high central nervous system half-life estimated to be many years. As a result, despite the observation of urinary Hg excretion in our study with dental amalgam exposure, Hg exposure from dental amalgams significantly contributes to Hg body burden.[19]

Strengths/limitations

In considering our study, the design utilized in the parent study was strong, and its strength helped to reduce any potential limitations. The overall design of the parent was constructed a priori to the actual examination of any study subjects, and the study subjects examined were randomly assigned to dental amalgam or composite groups at baseline. As a result, potential biases regarding potential reasons for exposure to a specific treatment or regarding specific types of evaluations undertaken on study subjects should not have adversely impacted the data analyzed. In addition, the sizes of both the amalgam and composite groups were moderate and not numerically weighted in a direction (i.e. there were several hundred study subjects in both the amalgam and composite groups), so that these factors helped reduce potential biases regarding the sample composition.

After initial random assignment of study subjects to amalgam/composite groups, the study subjects then had detailed information collected regarding specific biological parameters at baseline. Subsequently, detailed information was collected regarding exposure to dental amalgams (i.e. size, number, location, etc.) and repeated measurements of specific biological parameters. As a result, the repeated measurements examined in our study were collected in a controlled fashion, so that potential limitations, such as changes in sample collection techniques or analysis over the course of multiyear study of study subjects, should have minimally impacted the data collected.

Among the limitations of our study, it included minimal information regarding past exposure to Hg or other sources of Hg exposure during the study among the study subjects. As a result, it is possible that these unaccounted for sources of Hg may have created confounding in the data examined, helping to reduce the significance of the findings observed.

Despite this potential, our study found significant correlations. Our study has the limitation that only individuals who were healthy at initial presentation were allowed entry into the parent study. As a result, the biological effects of dental amalgam exposure observed in our study may reflect those specific to healthy individuals, and not necessarily the consequences of Hg exposure from dental amalgams in less-than-healthy individuals. Another potential limitation of our study is the length of follow-up. Study subjects were followed for only 8 years in the parent study. Hence, it was not possible to evaluate the potential long-term consequences of dental amalgam exposure over the course of decades in these individuals. Despite this fact, over the course of the 8 years of our study, Hg exposure from dental amalgams did significantly impact urinary Hg levels. A further potential limitation of our study was the moderate size of the sample examined. It is possible that with a larger sample size, the correlations observed would be more robust, and hence, even less likely to be the result of chance. In addition, another limitation of our study was that CDC's BMI 50th percentile clinical growth charts were utilized on the subjects examined. It is possible that there may be differences in the BMIs between children in the United States and Portugal, but given that the BMI data was applied equally to subjects regardless of their dental status, this should not have impacted the overall direction of the results observed. Our study also had other potential limitations. We were unable to quantitatively measure certain factors, such as smoking, chewing of solid foods, chewing gum, drinking hot drinks, and so on, which may increase the release of Hg from dental amalgams. Similarly, our study was not able to account for position and/or removal of dental amalgams, which can significantly increase Hg exposure. As a result, our study may underestimate the full extent of dental amalgam's contribution to urinary Hg levels. Finally, a limitation of our study was that Portugal is known for its high seafood consumption, and as a result of this higher baseline exposure to Hg probably somewhat reduced the significance of the results observed; and in cultures with less seafood consumption, the effects of Hg exposure from dental amalgams may be more striking.

Conclusion

The results of our study suggest that extent of Hg excretion in the urine is related to the exposure from dental amalgams in a dose-dependent fashion. The findings from our study are consistent with previous studies examining Hg exposure from dental amalgams and indicate that dental amalgams contribute to continuous Hg exposure in recipients. Future studies should be conducted to further evaluate the relationship between urinary Hg levels and other types of potential biomarkers and measurements of clinical symptoms using our statistical model.

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