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Chelated lead and bone lead

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TELL I, SOMERVAILE LJ, NILSSON U, BENSRYD I, SCHÜTZ A, CHETTLE DR, SCOTT MC, SKERFVING S. Chelated lead and bone lead. *Scand J Work Environ Health* 1992;18:113-9. In this study a close correlation [correlation coefficient (r) = 0.86, $P < 0.001$] was found between the blood lead level of 20 lead workers and their urinary excretion of lead for 24 h after intravenous infusion with 1 g of the chelating agent calcium disodium edetate. In addition, there were significant associations between lead levels in different bones (tibia/calcaneus: $r = 0.93$, $P < 0.001$; tibia/phalanx: $r = 0.67$, $P < 0.002$; calcaneus/phalanx: $r = 0.80$, $P < 0.001$), as measured by in vivo X-ray fluorescence. Chelation produced no significant change in the lead level in either tibia or calcaneus. There was a significant correlation between chelated lead and bone lead (eg, for calcaneus, $r = 0.62$) in currently exposed workers. However, there was no significant relationship when a retired worker and an inactive worker were included ($r = 0.14$). It was concluded that chelatable lead mainly reflects the blood and soft-tissue lead pool, which is only partly dependent upon the skeletal lead content that comprises the biggest share of the total body burden.

Key terms: blood, calcaneus, calcium disodium edetate, finger bone, occupational, phalanx, skeleton, tibia, urine, X-ray fluorescence.

Lead is an ubiquitous metal that is still widely used industrially. Once inside the body, it can be incorporated into the skeleton, where the turnover is slow compared with that in the blood and soft tissues. One method of assessing lead exposure is to use chelation techniques. Thus a chelating agent such as penicillamine (PCA) can be administered orally (1), or the intravenous administration of calcium disodium edetate (CaNa₂EDTA) can be used (2). Increased levels of excreted urinary lead are then used as an indicator of an excess body burden (3). In addition, chelation has been used therapeutically in cases of lead poisoning, especially among children (4), for whom it is assumed that chelation causes an overall reduction of the lead body burden. However, the relative inputs from the body compartments, such as soft tissue and bone, to the measured chelated lead output in urine have not been established.

Because over 90% of the body burden of lead is in the skeleton (5), a more direct measure of this burden in vivo is the assessment of skeletal content from measurements of the lead levels of various bone sites, either by biopsy or by the noninvasive technique of

X-ray fluorescence. Lead levels in the mainly cortical phalanx were first measured in occupationally exposed workers with the use of the gamma-ray source ⁵⁷cobalt to fluoresce the K-shell X rays of lead (6). An alternative method, developed more recently, is to use the gamma rays of ¹⁰⁹cadmium to fluoresce the K-shell lead X rays, the initial measurement being on the cortical midshaft of the tibia (7). Since the latter technique is self-normalizing to bone mineral and is independent of geometry and overlying tissue depth, it is applicable to any superficial bone site and has been extended to the measurement of lead levels in the trabecular calcaneus, or heel bone (8), and in the skull frontal bone. In addition, tibia lead levels have also been measured by fluorescence of the lower energy L-shell X rays (9), which, because of the short attenuation length of L-shell X rays, samples the lead in the outer few millimeters of the bone only.

Lead levels in cortical bone, as measured by X-ray fluorescence, have been shown to be a good index of cumulative past exposure, both in finger bone (10) and in tibia (11). However, the relationship between chelatable lead and bone lead levels remains unclear. In recent reports, associations were found between CaNa₂EDTA-chelated lead and tibia lead levels predicted by L-shell (12) and K-shell (13) X-ray fluorescence. However, in a similar study, PCA-chelatable lead was not related to the lead levels predicted by K-shell X-ray fluorescence for finger bone, while there was an association with biopsy specimens from the vertebra (14). Moreover, there were associations between CaNa₂EDTA-chelated lead and biopsies from the ileum (15).

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In this paper we report on the lead levels measured, by K-shell X-ray fluorescence, in the phalanx, tibia, and calcaneus of 20 occupationally exposed volunteers, who underwent simultaneous diagnostic CaNa_2EDTA chelation.

Subjects

The 20 male volunteers involved in this study were from the work force of a secondary lead smelter in southern Sweden. Their mean age was 46 (range 21–71) years, with a mean exposure time of 14 (range 1–40) years. One of the group had been retired for six years, and another had been removed from active lead work 11 years previously. Four subjects were studied in September 1986 and the remainder in December 1986. The subjects were, in fact, drawn from a larger study population, made up of volunteers for an earlier survey conducted on the same work force, the results of which have been reported elsewhere (16). Therefore the volunteers for this study could be selected so as to represent as wide a variation as possible in terms of the lead levels in tibia, heel, and phalanx.

Biochemical analyses of blood and urine samples taken at the time of the study were used to identify any health problems. Blood levels of hemoglobin, as well as serum levels of creatinine, aspartate aminotransferase, alkaline phosphatase, urate and phosphorous, were all within reference limits for all of the subjects. However, one subject had a slightly raised level of alanine aminotransferase of $0.9 \mu\text{kat} \cdot \text{l}^{-1}$, and two subjects had slightly increased levels of gamma glutamyl transferase of up to $1.2 \mu\text{kat} \cdot \text{l}^{-1}$. Two subjects had high levels of serum calcium (up to $2.9 \text{ mmol} \cdot \text{l}^{-1}$) and three subjects had between 2 and 4 mg albumin $\cdot \text{mmol}^{-1}$ creatinine in the urine.

The project was approved by the Ethical Committee of Lund University and all of the subjects gave their written consent.

Experimental procedures

Blood lead levels

For the determination of the blood lead concentration, venous blood was obtained immediately before CaNa_2EDTA administration from the cubital vein in metal-free heparinized tubes. Five-milliliter samples were wet-ashed, and the lead was complexed with dithione, extracted, and determined by flame atomic absorption spectrometry (17, 18). The detection limit was $10 \mu\text{g} \cdot \text{l}^{-1}$ ($0.05 \mu\text{mol} \cdot \text{l}^{-1}$).

Each analytical series contained six samples, two blanks containing reagents only and four "normal" blood samples (two with standard lead addition). Each sample was analyzed in duplicate, in different series. The coefficient of variation, as calculated from duplicate analyses, was as follows: 10% for 24 samples con-

taining $100 \mu\text{g} \cdot \text{l}^{-1}$ or less, 3.3% for 21 samples containing $100\text{--}200 \mu\text{g} \cdot \text{l}^{-1}$, 2.8% for 87 samples containing $200\text{--}400 \mu\text{g} \cdot \text{l}^{-1}$, and 2.3% for 15 samples containing $400\text{--}700 \mu\text{g} \cdot \text{l}^{-1}$.

The accuracy of the method has been tested in an inter-Nordic laboratory calibration program comprising eight reference blood samples twice a year. On the two calibration occasions, which included the period during which the present samples were analyzed, the results averaged 97.1 (SD 3.7, range 90–103, in different samples)% of the mean of other participating laboratories. The regression function of our results (Y , $\mu\text{g} \cdot \text{l}^{-1}$) on the average results of the other laboratories (X) was $Y = 1.025X - 16$ for the concentration range $120\text{--}700 \mu\text{g} \cdot \text{l}^{-1}$. The coefficient of linear correlation was 0.999. Furthermore, we participated in the UK External Quality Assessment Scheme, comprising one sample each second week. Our results, by single determinations on 30 samples, from a period which covered about half a year before and after the period of the present analyses, averaged 99.8 (SD = 4.6, range 90–108)% of the mean of the other laboratories. The regression function was $Y = 1.08X + 39$ for the concentration range $240\text{--}690 \mu\text{g} \cdot \text{l}^{-1}$. The coefficient of correlation (r) was 0.993.

Urinary lead levels

Urine was collected in acid-washed polyethylene bottles, and the volume and creatinine content were determined. The lead concentration of the urine samples was analyzed in duplicate in 5- to 20-ml samples (depending upon the expected concentration) by the method also used for the blood lead content. The detection limit was $2 \mu\text{g} \cdot \text{l}^{-1}$. The precision, as calculated from duplicate analyses, was 10% in the range up to $20 \mu\text{g} \cdot \text{l}^{-1}$ ($N = 51$), 7% in the range $20\text{--}60 \mu\text{g} \cdot \text{l}^{-1}$ ($N = 55$), 6% in the range $60\text{--}200 \mu\text{g} \cdot \text{l}^{-1}$ ($N = 14$), and 3% above $200 \mu\text{g} \cdot \text{l}^{-1}$ ($N = 33$).

The accuracy was tested with analyses of 20-ml samples of two commercial urine reference samples (Lanorm R, Behring Institute; metals 1, lot number 625203; metals 2, lot number 625303). Our results averaged 10 (SD 0.4, range 10–11) $\mu\text{g} \cdot \text{l}^{-1}$ ($N = 13$) and 120 (SD 3, range 120–130) $\mu\text{g} \cdot \text{l}^{-1}$ ($N = 12$), respectively, which was in good agreement with the assigned values of 10 (confidence range 8–12) $\mu\text{g} \cdot \text{l}^{-1}$ and 120 (confidence range 110–140) $\mu\text{g} \cdot \text{l}^{-1}$.

Chelated lead

A lead mobilization test (2) was performed in September and December of 1986. First, the bladder was emptied. Then 1 g of CaNa_2EDTA was infused intravenously in 500 ml of 5% glucose during 30 min. All of the urine was collected for 24 h.

Skeletal lead

Lead levels were determined for the middle part of the second phalanx of the left forefinger of 19 out of the 20 volunteers before chelation, in September 1986. These bone lead levels were assessed by in-vivo X-ray fluorescence with ^{57}Co as the radiation source (6, 10, 19, 20). The measurement time was 1800 s. The source activity was 0.6 GBq, giving a maximum skin dose of 3 mGy. The measurement error was typically $25 \mu\text{g lead} \cdot \text{g}^{-1}$ bone mineral. The accuracy was good when the results were compared with those obtained with atomic absorption spectrometry, and the precision of the method was about 15% (10).

The technique used for measuring finger-bone lead gave the measured concentration in readings per unit mass of wet cortical bone. To convert into readings per unit mass of bone mineral, we used a conversion factor of 1.72 (1/0.58). This factor was valid for cortical bone with a bone mineral concentration of 58%, by wet weight (21).

Lead levels in the middle part of the left tibia and the lower rear portion of the left calcaneus were assessed, both before and after chelation, for all of the subjects. Both bone sites were measured with an X-ray fluorescence technique, but with ^{109}Cd as the radiation source (7, 8). Four of the volunteers were monitored in September of 1986, when the tibia and calcaneus were measured simultaneously, both for 1800 s. With the tibia lead measurement the source activity was 5.7 GBq, giving a maximum skin dose of 1.2 mGy. The source activity for the calcaneus measurement was slightly higher, being 6.9 GBq, giving a maximum skin dose of 1.5 mGy. The remaining 16 subjects were measured pre- and postchelation in December of 1986, when the tibia and calcaneus measurements were made sequentially. The more active ^{109}Cd source, which had decayed to 6.0 GBq, was used with measurement times of 1800 s for the calcaneus and 1000 s for the tibia. The calcaneus measurement errors were typically $\pm 12 \mu\text{g lead} \cdot \text{g}^{-1}$ bone mineral, while the tibia measurement, being a dense bone, had a typical error of $\pm 7 \mu\text{g lead} \cdot \text{g}^{-1}$ bone mineral. Again, this technique yielded good accuracy when compared with the results obtained with atomic absorption spectrometry (22).

Statistical analyses

BMDP (biomedical data package) and SAS (statistical analysis system) statistical packages were used for fitting nonlinear functions to the chelated urinary lead values. These packages compute the least squares estimates of the parameters by a modified Gauss-Newton algorithm, given the function and the explicit form of the derivatives with respect to the parameters. The estimates of the parameters, their estimated asymptotic standard deviations, and the Pearson correlation coefficient between the observed and predicted values

of chelated urinary lead were calculated for each model.

Results

The tibia lead levels measured pre- and postchelation remained unaltered, the mean of the (postchelation minus prechelation) measurement being -1.7 (SD 13.9) $\mu\text{g lead} \cdot \text{g}^{-1}$ bone mineral. With the calcaneus measurement there did appear to be a slight decrease in the lead level after chelation [-11.5 (SD 24.1)], but this change did not achieve a high level of significance and therefore should not be regarded as a real decrease.

A summary of the study data, in terms of the average and range of values observed for the blood, bone, and chelated urinary lead levels, is given in table 1. The tibia and calcaneus lead levels correlated very strongly with each other ($r=0.93$, $P<0.001$). In addition, the phalanx concentrations correlated with the tibia ($r=0.67$, $P=0.002$) and calcaneus ($r=0.80$, $P<0.001$) levels. Using simple linear correlations, we found a close association between the blood lead level before chelation and the 24-h chelated urinary output ($r=0.86$, $P<0.001$) (figure 1).

If the chelated urinary lead is explained solely by an exponential function of blood lead (BPb) (through

Table 1. Lead levels in blood and bone, and lead excretion in urine following chelation with calcium disodium edetate, in 20 lead workers.

	Mean	Range
Blood lead ($\mu\text{g} \cdot \text{l}^{-1}$)	366	200–550
Chelated urinary lead ($\mu\text{g} \cdot 24 \text{ h}^{-1}$)	916	170–1650
Bone lead ($\mu\text{g} \cdot \text{g}^{-1}$ bone mineral)		
Tibia	48	–5–193
Calcaneus	130	–8–430
Phalanx ^a	72	9–180

^a Based upon 18 measurements.

Figure 1. Lead levels in blood and lead excretion in urine during the 24 h following chelation with calcium disodium edetate for 20 lead workers. A retired worker and one removed from active work are denoted by circles.

the origin), with the units given in table 1, the predicted relationship is

$$\text{chelated lead} = 522 (e^{0.00263 \text{ BPb}} - 1). \quad (\text{equation 1})$$

However, all of the bone lead values showed poor associations with both the blood lead (tibia: $r = 0.005$, $P = 1.0$; calcaneus: $r = -0.06$, $P = 0.8$; finger: $r = -0.17$, $P = 0.5$) and chelated urinary lead levels. As an example of the latter, the relationship between calcaneus lead and chelated urinary lead is shown in figure 2, for which the correlation was $r = 0.14$ ($P = 0.6$). For the tibia and the phalanx the correlations were $r = 0.14$ ($P = 0.6$) and $r = -0.01$ ($P = 1.0$), respectively.

An interesting point to note is that the worker who had been retired for six years (marked separately in figure 2) produced the lowest chelated urinary lead, but had one of the highest levels of bone lead. A similar outlier (also marked in figure 2, "worker 353") was a worker who had been permanently removed from heavy lead exposure some 11 years before the study. His average blood lead value for the five-year period prior to this change was $730 \mu\text{g} \cdot \text{l}^{-1}$, which dropped to $500 \mu\text{g} \cdot \text{l}^{-1}$ in the five-year period thereafter, and was $200 \mu\text{g} \cdot \text{l}^{-1}$ at the time of the study (the lowest recorded level of all 20 subjects).

If a linear term for lead in each type of bone (tibia, calcaneus, and phalanx) is added separately to blood, as the explanatory variable, then the exponential coefficient

for blood in each case is similar to that obtained when blood is considered to be the only explanatory variable (table 2). However, none of these linear skeletal terms is well defined (all have estimated standard deviations of similar magnitude to the slope estimate). In the case of the best of these (finger), the correlation between the measured chelated urinary lead and that predicted by the multivariate model was a correlation coefficient of 0.85 compared with one of 0.83 for equation 1. The predicted chelated urinary lead was the sum of the contribution from the blood term and the bone term. The percentage contribution from the linear finger term had an average (for the 19 workers) of only 6 (range 1–27)%.

It is interesting to note that when an alternative modeling procedure is used, similar conclusions are reached:

$$\text{chelated lead} = 2.03 (\text{BPb})^{1.69}. \quad (\text{equation 2})$$

If the bone lead levels are added individually to the model, there is only a marginal, nonsignificant, increase in the correlation coefficient between the measured and predicted chelated lead (eg, the correlation coefficient changes from 0.84 to 0.86). Again, with this model, the contribution of bone lead to chelated lead was not well defined, but was less than 20%, in agreement with the results of the exponential model.

Discussion

This study was designed to investigate the relationship between chelated urinary lead after the intravenous administration of CaNa_2EDTA and the lead body burden. The distribution of lead within the body can be considered to be represented by several compartments (23), including the blood and soft tissues, which are in rapid equilibrium with the blood, and the relatively immobile bone fraction. Each of these compartments can, however, be further subdivided. For example, the blood not only contains the erythrocyte-bound lead, but also the more readily exchangeable serum lead.

Most of the body burden is in the skeleton. There are, however, differences in calcium metabolic activity between different bone types [eg, trabecular and cortical (24, 25)], which was assumed would be reflected in lead turnover rates. Hence, in deciding on the choice

Figure 2. Lead levels in calcaneal bone and lead excretion in urine during the 24 h following chelation with calcium disodium edetate for 20 lead workers. A retired worker and one removed from active work are denoted by circles.

Table 2. Results of fitting an exponential function [$\text{UPb} = P_1 (e^{P_2 (\text{BPb})} - 1) + P_3 (\text{SPb})$] of blood lead (BPb) with and without an additional linear term for skeletal lead (SPb) to chelated urinary lead (UPb) for 20 smelter workers.

Skeletal lead	Number of workers	P1	SD for P1	P2	SD for P2	P3	SD for P3	Correlation coefficient
None	20	552	372	0.00263	0.00106	—	—	0.83
Tibia	20	405	292	0.00305	0.00118	1.19	1.18	0.84
Calcaneus	20	375	269	0.00316	0.00120	0.58	0.48	0.85
Phalanx	18	407	348	0.00301	0.00134	0.69	1.34	0.85

of bone sites for a study of lead uptake, of which this work forms a part, the calcaneus was chosen as a large trabecular bone to complement measurements in the largely cortical tibia and phalanx. The tibia and calcaneus lead levels correlated very strongly with each other; those of the phalanx also correlated with the tibia and calcaneus levels. In a larger, related study, involving measurements on active and retired workers having a wide range of exposure patterns, it was also found that there was a high correlation between the lead levels of the three bones and that the linear relationship between the pairs of bones and high bone lead levels was maintained. This finding suggests that the lead excretion rates (ie, the effective half-times) are comparable for calcaneus, tibia, and phalanx under normal conditions. The lead levels of the three bone sites will clearly be closely related to the total skeletal and, hence, body burden.

Simple single-variable linear correlations do not adequately describe the real underlying relationships between blood or bone lead and chelated urinary lead. For example, although the linear relationship between blood lead and chelated urinary lead is convincing, the statistically significant offset produced is unlikely to be physiologically accurate. In addition, we note that previous work, using PCA as the chelating agent and a 6-h urine collection period (14), showed the applicability of an exponential model over a wide range of lead exposure conditions. If the data from the present survey are considered together with data from other studies (26, 27), which have involved the intravenous administration of CaNa_2EDTA at a dose of approximately 1 g, a nonlinear relationship is obvious (figure 3), the relative increase of chelated urinary lead increasing with rising blood lead levels.

In the present small study, the information available relates only to the lead concentration of the whole blood and the three bone sites, with no information at all concerning the soft tissues. The use of assumed data for the soft-tissue compartment and other pool sizes adds only to the uncertainties, and therefore the construction of a multicompartiment model, based on such limited data, becomes so ill defined as to be inappropriate. Instead, a simple nonlinear model has been applied to the bone, blood, and chelated urinary lead data, with no allowance for pool size or the presence of a separate soft-tissue compartment.

The blood lead level displayed a close correlation with the chelated urinary lead level. In the case of the association between chelated urinary lead and bone lead, the relationship showed only a poor, nonsignificant linear correlation. This finding suggests that chelated lead is not, in general, a good indicator of total body burden, as has often been claimed, and that good correlations are only likely to be observed for subjects with comparable exposure status. The chelated lead concentration therefore reflects that part of the body burden that is more readily mobilized, and it is likely to be equivalent to the more exchangeable lead

Figure 3. Lead levels in blood and lead excretion in urine during the 24 h following chelation with calcium disodium edetate for the 20 lead workers of this study (circles). Data from Greenburg et al (27) (crosses) and Araki & Ushio (26) (squares) have been included for comparison.

pools in the body, namely, the blood and the soft-tissue pools and an actively exchangeable bone fraction, the latter comprising the more trabecular bones, such as vertebra (14) and rib, and the surface layers of the cortical bones.

We note that, for worker 353 and the retired worker present in figures 1 and 2, the chelated urinary lead level was low, but the bone lead levels were high. A similar pattern was observed in a previous study (14) comparing chelated lead with the lead content of either finger bones or vertebral bone biopsies. These results would suggest that, although the lead body burden was substantial, the exchangeable fraction of burden accessible to chelation was very reduced by recent low exposure levels. Again, this possibility indicates that the bone lead levels per se relate to chelated urinary lead in a complex way and that looking for correlations without being able to take into account exposure history (ie, using a metabolic model) is unlikely to be fruitful. For example, it is possible that the 10–20% of chelated lead that can be correlated with bone lead may be associated with that part of the blood lead known to have a long residence time (28). In other words, a fraction of the blood lead can be considered to be deriving from the bone lead pool.

As noted in the introduction, there have been studies examining the relationship between chelated urinary lead and vertebral lead (14) and cortical surface lead (12). In the former study, the correlation observed was $r = 0.81$ ($N = 11$) for active workers and $r = 0.91$ ($N = 12$) for retired workers; for the combined data set the value was $r = 0.53$ ($N = 23$). In the latter study, Wielepolski et al (12) found a correlation coefficient of 0.69 ($N = 34$) for active workers. These correlations are both much stronger than were observed for our complete data set for any of the bones measured. However, if we exclude both the retired worker and the one removed from active lead work (on the grounds that the lead distribution between different pools may have been different from that of currently active workers),

then the correlation between calcaneus and chelated lead, for example, increases significantly, to $r = 0.62$ ($N = 18$). Recently, rather poor associations were reported between CaNa_2EDTA -chelated lead on one hand and either finger lead in patients with renal impairment (29) or tibia lead in lead workers (13) on the other, while there was a rather good correlation with lead in ileum biopsies (15).

Since the actual amounts of lead excreted during the 24-h postchelation period are small in comparison with the total skeletal lead burden [in the region of 600 mg for an occupationally exposed adult (5)], it is of course not surprising that the bone lead levels measured pre- and postchelation did not show a significant decrease, outside the errors associated with the measurements.

In conclusion, in attempts to include both blood and bone lead in a model to explain chelated urinary lead, it would seem that, in adults under constant exposure conditions, only a small fraction of the chelated urinary lead derives from the bones. Although the data set is small and the model not well defined, it once again supports the argument that chelated urinary lead does not reflect the total body burden of lead, but only that fraction of it which is mobilized. It can, however, be argued that this is the more physiologically accessible fraction and is therefore of more clinical relevance in assessments of the effects of lead than the body burden itself is.

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