Sequential Measurements of Bone Lead Content by L X-Ray Fluorescence in CaNa$_2$EDTA-Treated Lead-Toxic Children

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With the development of L X-ray fluorescence (LXRF) to measure cortical bone lead directly, safely, rapidly, and noninvasively, the present study was undertaken to a) evaluate LXRF as a possible replacement for the CaNa$_2$EDTA test; b) quantify lead in tibial cortical bones of lead-toxic children sequentially following one to two courses of chelation therapy. The clinical research design was based upon a longitudinal assessment of 59 untreated lead-toxic children. At enrollment, if the blood lead (PbB) was 25 to 55 µg/dL and the erythrocyte protoporphyrin (EP) concentration was ≤ 35 µg/dL, LXRF measurement of tibial bone lead was carried out. One day later, each child underwent a CaNa$_2$EDTA provocative test. If this test was positive, lead-toxic children were admitted to the hospital for 5 days of CaNa$_2$EDTA therapy. These tests were repeated 8 weeks and 6 months after enrollment. Abatement of lead paint hazards was achieved in most apartments by the time of initial hospital discharge.

The LXRF instrument consists of a low energy X-ray generator with a silver anode, a lithium-doped silicon detector, a polarizer of incident photons, and a multichannel X-ray analyzer. Partially polarized photons are directed at the subcutaneous, medial mid-tibial cortical bone. The LXRF spectrum, measured 90° from the incident beam, reveals a peak in the 10.5 KeV region, which represents the lead La line. The effective dose equivalent using tissue weighting factors according to guidelines of the National Council on Radiation Protection and Measurements (1989), was 2.5 µSv. The reproducibility of replicate LXRF measurements, including the day-to-day variation of the instrument, in 28 lead-toxic children, after repositioning the instrument within 5 cm of the first LXRF measurements, was 9.2 (95% confidence limits). For an overlying tibial skin thickness of 5 mm, the minimum detection limit was 7 µg of lead (wet weight) at the 95% confidence interval.

Based upon a discriminant analysis, 80% of lead-toxic children were predicted correctly as being CaNa$_2$EDTA-positive or CaNa$_2$EDTA-negative. Using LXRF and PbB values to predict CaNa$_2$EDTA outcomes, the specificity and sensitivity of these two predictors were 98 and 92%, respectively. In a significant fraction of CaNa$_2$EDTA-positive and CaNa$_2$EDTA-negative children, cortical bone lead values were similar to lead concentrations measured via bone biopsy in normal adults and lead workers in industry. By 24 weeks after enrollment, PbB, EP, and primary lead/EDTA ratios were similar in all groups. The most dramatic decreases in not corrected photon counts by LXRF occurred in children treated twice. Mean values of cortical bone lead by LXRF at 24 weeks in all three groups of children were similar to the mean concentration in untreated CaNa$_2$EDTA-negative children at enrollment but still three to five times greater than those measured in the tibial or whole teeth of normal European children using atomic absorption. In lead-toxic children who did not qualify for treatment, additional significant accumulation of lead in bone ended once children were removed from leaded environments or returned to lead-abated apartments. These data suggest that LXRF measurements of lead in tibial cortical bone have considerable promise to replace the CaNa$_2$EDTA test and to provide a more appropriate end point of chelation therapy than the conventional indices of PbB and EP. Moreover, markedly elevated bone lead values accumulated during early childhood may have an intergenerational impact, as maternal lead stores amassed during childhood cross the placenta and directly affect the developing fetus.

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Introduction

Lead toxicity is the most common preventable disease in preschool children today in the United States. In its 1988 report to Congress, the U.S. Public Health Service estimated that 5 million or more young children are at risk from all sources of lead, including paint and lead in food, drinking water, dust, dirt, and gasoline (1). This disease is likely to continue for many years because there are still about 40 million dwellings nationally with hazardous leaded paint (1).

Neurobehavioral (2,3), cognitive (2,3), developmental (4,5), and biochemical abnormalities (6) have been demonstrated in children with blood lead (PbB) levels below 25 μg/dL, the Centers for Disease Control's current definition of an upper limit for "normal" PbB values (7). Present screening and diagnostic techniques cannot identify large numbers of asymptomatic lead toxic children, many of whom may require chelation therapy. Erythrocyte protoporphyrin (EP) screening identifies only about one-half of lead-toxic children who, by definition, have elevated PbB values between 25 and 55 μg/dL (8). Furthermore, the residence half-time of lead in blood is short and reflects recent exposure (9), whereas bone lead represents a time-averaged compartment of lead with a residence time of months to years (10).

The decision to proceed with in-hospital chelation therapy is based upon a positive disodium calcium edetate (CaNa₂EDTA) test (11), which is the current reference method for assessing total body lead stores (12). CaNa₂EDTA chelates lead from extracellular fluid, thereby removing lead from hard and soft tissues, including blood (12). The CaNa₂EDTA test requires a quantitative 8- to 24-hr urine collection, which is virtually impossible to achieve in large numbers of young children.

With the recent development of L X-ray fluorescence (LXRF) to measure cortical bone lead directly, safely, rapidly, and noninvasively (13,14), the present study was undertaken to: (a) evaluate LXRF as a possible replacement for the CaNa₂EDTA test (13); (b) quantify lead in tibial cortical bones of mildly to moderately lead-toxic children before treatment (13); and (c) quantify lead in tibial cortical bones of lead-toxic children sequentially following one to two courses of chelation therapy.

Methods

The clinical research design was based upon a longitudinal assessment of 59 untreated lead-toxic children. At enrollment, PbB values were determined. If the PbB was 25 to 55 μg/dL and the EP concentration in whole blood was ≥ 35 μg/dL, LXRF measurement of tibial bone lead was carried out (Fig. 1). One day later, each child underwent a CaNa₂EDTA provocative test. If this test was positive, lead toxic children were admitted to the hospital for 5 days of CaNa₂EDTA therapy at a daily dose of 1000 mg/m² given by continuous intravenous infusion. These tests were repeated 6 weeks and 6 months after enrollment. During this 6-month period, if a child qualified for a second provocative test and a second course of CaNa₂EDTA treatment in the hospital, such regimens were carried out. Abatement of lead paint hazards was achieved in most apartments by the time of initial hospital discharge. In about 20% of children, alternative housing was obtained with family or friends until housing repairs were completed. By 6 to 8 weeks postenrollment, most of the major housing repairs had been completed.

The LXRF instrument consists of a low-energy X-ray generator (Philips Electronics Model PW1729-25) with a silver anode, a lithium-doped silicon detector for the incident beam, reveals a peak in the 10.5 KeV region, which represents the lead Lα line. To correct for attenuation of photons by pretibial soft tissue, thickness measurements were carried out ultrasonically.

The average skin dose, deliberately limited to 1 rad over a 4-cm² area, was delivered in 16.5 min (Table 1). The effective dose equivalent was calculated to be ≤ 2.5 microsieverts, about 1/10th to 1/20th of one dental X-ray and about 1/25th of that from one radiographic examination of the chest (13,14). This effective dose equivalent is < 0.1% of the average annual effective dose equivalent for an individual in the U.S. population from natural background radiation sources. Within the same population, therefore, LXRF measurements of the tibia are much less risky than those for dental and pulmonary radiological examinations that
are performed routinely. Because this instrumentation was designed as an essentially closed system, a parent can be present during the LXRF examination with negligible risk from scattered radiation. The reaction was designed as an essentially closed system, a parent can be present during the LXRF examination within 5 cm of the first LXRF measurement, was obtained from regression analyses of these ratios with respect to soft tissue thickness (13).

To quantify X-ray attenuation by overlying soft tissue, the net 16.5-mm photon count in the lead Lα peak from the medial aspect of the tibia of nine adult surgical specimens was recorded before and after removal of the bone. An average effective exponential attenuation coefficient (0.45 ± 0.06 mm-1, mean ± SEM) was calculated from the resultant nine photon count ratios (13). Similar results were obtained from regression analyses of these ratios with respect to soft tissue thickness (14).

The average concentration of lead in the full cross-section of tibial bone adjacent to the area of LXRF examination was measured by several flameless atomic absorption measurements of dissolved bone from each of nine amputated specimens. The correlation coefficient (r value) between LXRF measurements of bone lead and the average value of atomic absorption analyses of two full cross-sections of each specimen was 0.92 (14). The relative standard deviation for 18 measurements of bone lead samples by flameless atomic absorption spectroscopy (AAS) was ± 5.1% (95% confidence limit). The r value between LXRF measurements of intact limbs and AAS measurements of bone lead, corrected for 5 mm of overlying soft tissue in all study children, was about two times greater in CaNa2EDTA-negative children (Table 3) (13). Values for bone lead, corrected for 5 mm of overlying soft tissue in all study children, were about two times greater in CaNa2EDTA-negative children than in CaNa2EDTA-positive children. Correlation coefficients other than the correlation between LXRF and EP were statistically significant (Table 4) (13). Discriminant function analysis was carried out in progress (13,14).

Results

Based upon clinical research data already published (13), sequential LXRF data presented herein and a detailed study of the physics and calibration of the LXRF instrument (14), the validation and diagnostic applicability of this new technique have been established in lead-toxic children (Table 2). Nonetheless, further instrument improvements to decrease the counting time and enhance the minimum detection limit (MDL) below 7 ag lead/g of bone can be anticipated by modifying the geometry of the detector and using different polarizing materials (Table 2). Dosimetry measurements have also been carried out to assess the safety of LXRF measurements during pregnancy. These data indicate that one or two LXRF measurements during pregnancy is equivalent to the natural background radiation dose that the fetus is exposed to during 15 min of normal gestation (15).

Table 1. LXRF technique: noninvasive detection of bone lead in core using polarized radiation.

| Parameter                      | Carried out | In progress |
|--------------------------------|-------------|-------------|
| Clinical relevance             | X           |             |
| Dosimetry                      | X           |             |
| Reproducibility                | X           |             |
| Reproducibility in lead-toxic  | X           |             |
| children                       |             |             |
| AAS versus LXRF (surgically    | X           |             |
| removed limbs                  |             |             |
| Minimum detection limit        | X           |             |
| Exponential attenuation        | X           |             |
| coefficient                    |             |             |
| Photon count ratio             | X           |             |
| Regression analysis            |             |             |
| Radiation dose (15)            | X           |             |
| Further improvements in system |             |             |
| Counting time                  | X           |             |
| Lead/strontium ratio           | X           |             |
| Minimum detection limit        | X           |             |

Table 2. Criteria for validation and clinical assessment of LXRF measurements in lead-toxic children (13,14).

| Parameter                      | Carried out | In progress |
|--------------------------------|-------------|-------------|
| Clinical relevance             | X           |             |
| Dosimetry                      | X           |             |
| Reproducibility                | X           |             |
| Reproducibility in lead-toxic  | X           |             |
| children                       |             |             |
| AAS versus LXRF (surgically    | X           |             |
| removed limbs                  |             |             |
| Minimum detection limit        | X           |             |
| Exponential attenuation        | X           |             |
| coefficient                    |             |             |
| Photon count ratio             | X           |             |
| Regression analysis            |             |             |
| Radiation dose (15)            | X           |             |

Based upon home visits and objective assessments of the quality of housing of these Bronx children, their ages, and their PbB, EP, and urinary lead-CaNa2EDTA ratios (PbU/EDTA), these lead-toxic children were representative of the majority of children attending lead-toxicity programs nationally. The CaNa2EDTA-positive children had higher PbB, EP, and urinary lead-CaNa2EDTA ratios than PbB/EDTA-negative children (Table 3) (13). Values for bone lead, corrected for 5 mm of overlying soft tissue in all study children, were about two times greater in CaNa2EDTA-negative children than in CaNa2EDTA-positive children.

Correlation coefficients other than the correlation between LXRF and EP were statistically significant (Table 4) (13). Discriminant function analysis was carried out in progress (13,14).
Table 3. PbB, EP, CaNa,EDTA values, and net corrected LXRF values in lead-toxic children (16).

| CaNa,EDTA test result | Age (months) | PbB, µg dL | EP, µg dL | Ratio of PbB/CaNa,EDTA | Net photon counts | Bone Pb, µg g
|------------------------|-------------|------------|-----------|------------------------|-----------------|--------------
| Negative (n = 30)      | 33 ± 10°    | 30 ± 5°    | 59 ± 43°  | 0.39 ± 0.13°           | 539 ± 26°       | 4 ± 2°
| Positive (n = 29)      | 38 ± 15°    | 39 ± 8°    | 115 ± 65° | 0.95 ± 0.27°           | 309 ± 52°       | 29 ± 4°

* Corrected according to the day-to-day reproducibility of the instrument.
* Corrected to 5 mm of overlying skin thickness.
* Mean ± SD
* Mean ± SEM
* p < 0.01 versus CaNa,EDTA negative group.

Table 4. Statistical analyses of net corrected LXRF photon counts, PbB, EP, and CaNa,EDTA test results from 59 lead toxic children (16).

| Pearson correlation coefficient | Analysis of tests |
|--------------------------------|-------------------|
|                                | PbB, EP           | LXRF, CaNa,EDTA | PbB/CaNa,EDTA | PbB |
| r                              | 0.188             | 0.200           | 0.472         | 0.701 | 0.499 |
| p                              | < 0.003           | > 0.010         | < 0.001       | < 0.001 | < 0.001 |

Table 5. CaNa,EDTA test outcomes compared to predicted outcomes from a discriminant analysis using corrected LXRF photon counts and PbB values as independent variables (13,14).

| Actual CaNa,EDTA outcomes | Predicted CaNa,EDTA outcomes |
|---------------------------|------------------------------|
| -                         | -                            |
| -                         | 26                            |
| 2                         | 25                            |

* By using not corrected LXRF photon counts and PbB to predict CaNa,EDTA test outcomes, the specificity (true negative / (true negative + false positive)) = 25/28 = 89% and the sensitivity (true positive / (true positive + false negative)) = 25/30 = 93%.

In this longitudinal study, lead-toxic children who did not qualify for treatment and other children who underwent one or two courses of CaNa,EDTA treatment were re-evaluated 6 weeks and 24 weeks postenrollment. By 24 weeks, PbB, EP, and PbU/EDTA ratios were very similar in all three groups (Figs. 2A-C). The most dramatic decreases in net corrected photon counts by LXRF occurred in children treated twice. In addition, there was a gradual and progressive dissociation between PbB, EP, or PbU/EDTA ratios and sequential measurements of bone lead by LXRF (Fig. 2D).

Mean values of cortical bone lead by LXRF at 24 weeks in all three groups of children were similar to the mean concentration in untreated CaNa,EDTA-negative children at enrollment and still three to five times greater than those measured in the tibia or whole teeth of normal European children using AAS (18-21). In lead-toxic children who did not qualify for treatment, additional significant accumulation of lead in bone ended once children were removed from leaded environments and/or returned to lead-abated apartments (Fig. 2D).

Discussion

The development and clinical validation of K-line XRF instruments in industrially exposed adults (22,23) and the L-line XRF technique in lead-toxic chil-
than to chemical difference between lead and calcium. A PbB determination and relevance and diagnostic capability of the LXRF technique have been proven. A PbB determination and relevance and diagnostic capability of the LXRF technique have been proven. It is clear from previous work that concentrations of lead in bone (long bones and tooth dentine) correlate more closely to skeletal remodeling and recycling rates than to chemical differences between lead and calcium.

In this study of 59 lead-toxic children, the clinical relevance and diagnostic capability of the LXRF technique have been proven. A PbB determination and LXRF measurement were predictive of the need for in-hospital chelation therapy in 96% of lead-toxic children (PbB: 25–55 μg/dL; EP ≥ 35 μg/dL). By including bone lead measurements by LXRF, several additional thousands of lead-toxic U.S. children annually could be correctly categorized and appropriately managed medically (1). Moreover, the capability of this new LXRF technique may be applied even more widely as considerations are given to lowering the current Centers for Disease Control's definition of an elevated PbB value as ≥ 25 μg/dL. In this regard, at mean PbB values of 33 and 35 μg/dL in CaNa₂EDTA-negative and CaNa₂EDTA-positive children, respectively, a majority of children in both groups, by 6 years of age, have already achieved bone lead values measured in normal adults and workers in lead industries. We surmise that either an excessively narrow margin of safety or insufficient safety is provided by current U.S. guidelines, which define an elevated PbB as ≥ 25 μg/dL.

Other results indicated that neither age nor EP contributed to the power of the discriminant analysis; a significant though modest correlation was observed between bone lead values by LXRF and PbB concentrations in untreated children. In children 6 months after enrollment who were untreated, treated once or treated twice (Figs. 2A–C), PbB, EP, and PbU/EDTA ratios returned to values currently considered to be normal. In contrast, talib cortical bone lead concentrations remained three to five times higher than concentrations in compact tooth bone in normal European children (18–21)(Fig. 2D). These high bone lead values, at the end point of so-called successful chelation therapy, may prove to be of considerable public health significance as some of these children become women of childbearing age. Elevated bone lead values accumulated during early childhood may have an intergenerational impact, as these maternal lead stores cross the placenta and impact directly on the developing fetus. These data indicate that LXRF measurements of lead in cortical bone may have the potential to replace the cumbersome, impractical CaNa₂EDTA test. Our results also suggest that LXRF measurements of lead in bone may ultimately prove to be a more appropriate endpoint of chelation therapy than the conventional indices: PbB, EP, and PbU/EDTA. We speculate that LXRF measurements may prove to be useful predictors of the results of neurobehavioral parameters in lead-toxic children after chelation therapy.

FiguRE 2. Sequential values for (A) PbB. (B) EP. (C) PbU/EDTA ratios, and (D) net corrected LXRF counts are shown in children at enrollment and 6 weeks and 6 months after enrollment. Rx = 0 indicates lead-toxic children who did not qualify for CaNa₂EDTA treatment; Rx = 1 represents children treated with one in-hospital course of CaNa₂EDTA after obtaining baseline values at enrollment, and Rx = 2 indicates lead-toxic children treated in the hospital with CaNa₂EDTA after baseline values were obtained at enrollment and again 6 weeks postenrollment.

Table 4. Cortical bone lead values in children.

| Reference          | Subjects | Mean, ppm wet weight |
|--------------------|----------|----------------------|
| Barry (18)         | Normals  | 3                    |
| Winnecke (19)      | Normals  | 3.5                  |
| Grandjean (20)     | Normals  | 3.5                  |
| Neeldeman (21)     | Lead poisoned | 31                  |
| Winnecke (21)      | Smaller exposed | 12                  |
| Rosen et al. (22)  | Lead toxic |                      |
| (by LXRF)          | CaNa₂EDTA -1 | 14                  |
|                    | CaNa₂EDTA +1 | 29                  |

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