

Sequential Measurements of Bone Lead Content by L X-Ray Fluorescence in CaNa₂EDTA-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 CaNa₂EDTA test; b) quantify lead in tibial cortical bones of mildly to moderately lead-toxic children before treatment; and c) 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 CaNa₂EDTA provocative test. If this test was positive, lead-toxic children were admitted to the hospital for 5 days of CaNa₂EDTA therapy. These tests were repeated 6 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 L_α line. The effective dose equivalent using tissue weighting factors according to guidelines of the National Council on Radiation Protection and Measurements (1988), was 2.5 µSv. The reproducibility of replicate LXRF measurements, including the day-to-day variation of the instrument, in 26 lead-toxic children, after repositioning the instrument within 4 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/g (wet weight) at the 95% confidence interval.

Based upon a discriminant analysis, 90% of lead-toxic children were predicted correctly as being CaNa₂EDTA-positive or CaNa₂EDTA-negative. Using LXRF and PbB values to predict CaNa₂EDTA outcomes, the specificity and sensitivity of these two predictors were 86 and 93%, respectively. In a significant fraction of CaNa₂EDTA-positive and CaNa₂EDTA-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 urinary lead/EDTA ratios were similar in all groups. The most dramatic decreases in net 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 CaNa₂EDTA-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 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 CaNa₂EDTA 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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Table 1. LXRF technique: noninvasive detection of bone lead *in vivo* using polarized radiation.

| | | |
|--|--|---------------------|
| X-ray generator | | |
| Voltage | 50 kVp | (Closed system; |
| Current | 30 mA | without significant |
| X-ray tube anode | Ag | scattering) |
| Detection system | | |
| X-ray detector | Si (Li) | |
| Patients | | |
| Age | 1-6 years | |
| Exposed area | ~4 cm ² | |
| Imparted energy | 0.1 mJ (~1/10-1/20 of dental X-ray) | |
| Effective dose equivalent | ≤ 2.5 μSv (~1/20-1/25 of chest X-ray) | |
| Counting time | 16.5 min | |
| Soft tissue (skin) thickness over the medial surface of the tibia | 3-8 mm (median, 5 mm) | |
| Minimum detection limit | 7 μg lead/g of bone with 5 mm of skin thickness | |
| Day-to-day instrument reproducibility | ± 5.1% (95% confidence interval) | |
| <i>In vivo</i> reproducibility of replicate measurements in 26 lead-toxic children | ± 9.2% (95% confidence interval) | |

the tibia are much less risky than those 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 reproducibility of replicate LXRF measurements in 26 lead-toxic children, after repositioning the instrument within 4 cm of the first LXRF measurement, was ± 9.2% (95% confidence limit) (13,14).

To quantify X-ray attenuation by overlying soft tissue, the net 16.5-min photon count in the lead L α peak from the medial aspect of the tibia of nine adult surgically amputated specimens was recorded before and after removal of epitibial soft tissue. An average effective exponential attenuation coefficient (0.45 ± 0.06 mm⁻¹, mean ± SEM) was calculated from the resultant nine photon count ratios (13,14). Similar results were obtained from regression and analyses of these ratios with respect to soft tissue thickness (15). The average concentration of lead in the full cross-section of tibial bone subjacent 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 bare bones and the average value of atomic absorption analyses of two full cross-sections of each specimen was 0.92 (15). The relative standard deviation for 18 measurements of bone lead samples by flameless atomic absorption spectroscopy (AAS) was ± 5.1% (95% confidence limits). The *r* value between LXRF measurements of intact limbs and AAS measurements of the bone lead samples was 0.95

Table 2. Criteria for validation and clinical assessment of LXRF measurements in lead-toxic children (13,14,15).

| Parameter | Carried out | In progress |
|--|-------------|-------------|
| Clinical relevance | X | |
| Dosimetry | X | |
| Closed system | X | |
| Parent in attendance | X | |
| Reproducibility of instrument | X | |
| Reproducibility in lead-toxic children | X | |
| AAS versus LXRF (surgically removed limbs) | X | |
| Minimum detection limit | X | |
| Exponential attenuation coefficient | X | |
| Photon count ratios | | |
| Regression analysis | | |
| Pregnancy-dosimetry (16) | X | |
| Further improvements in system | | X |
| Counting time | | |
| Lead/strontium ratios | | |
| Minimum detection limit | | |

(15). The average value of the ratio of the tibial bone lead concentration, in micrograms per gram, to the net corrected LXRF photon count, normalized to the median skin thickness of 5 mm, was 0.09 ± 0.01 (μg/g/count, mean ± SEM). For this skin thickness, the minimum detection limit was estimated to be 7 μg lead/g (wet weight) at the 95% confidence interval (13,14,15).

Based upon clinical research data already published (13,14), sequential LXRF data presented herein and a detailed study of the physics and calibration of the LXRF instrument (15), 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 μg 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 (16).

Results

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 net corrected LXRF photon counts compared to the CaNa₂EDTA-negative children (Table 3) (13,14). Values for bone lead, corrected for 5 mm of overlying soft tissue in all study children, were about two times greater in CaNa₂EDTA-positive than in CaNa₂EDTA-negative children.

Table 3. PbB, EP, PbU/CaNa₂EDTA values, and net corrected LXRF values in lead-toxic children (13,14).

| CaNa ₂ EDTA test result | Age, months | PbB, µg/dL | EP, µg/dL | Ratio of PbU/CaNa ₂ EDTA | Corrected LXRF values ^{a,b} | |
|------------------------------------|----------------------|---------------------|-----------------------|-------------------------------------|--------------------------------------|------------------------------|
| | | | | | Net photon counts | Bone Pb ^c µg Pb/g |
| Negative (n = 30) | 33 ± 10 ^d | 30 ± 5 ^d | 89 ± 43 ^d | 0.39 ± 0.13 ^d | 159 ± 20 ^e | 14 ± 2 ^e |
| Positive (n = 29) | 38 ± 15* | 39 ± 8* | 115 ± 65 [†] | 0.95 ± 0.27 [†] | 309 ± 52* | 29 ± 4* |

^a Corrected according to the day-to-day reproducibility of the instrument.

^b Corrected to 5 mm of overlying skin thickness. The normalization of these data to a standard epitibial soft tissue thickness of 5.0 mm in this table was carried out, but does not pertain to Table 2 (13,14).

^c Normal adult values for tibial lead are 19–27 µg Pb/g (17,18). Values for tibial lead in adult workers in lead industries are ≥ 30 µg Pb/g (17,18).

^d Mean ± SD.

^e Mean ± SEM.

* *p* < 0.001 versus CaNa₂EDTA-negative group.

† *p* < 0.01 versus CaNa₂EDTA-negative group.

Table 4. Statistical analyses of net corrected LXRF photon counts, PbB, EP, and CaNa₂EDTA test results from 59 lead toxic children (13,14).

| Pearson correlation coefficients | Analysis of tests | | | | |
|----------------------------------|-------------------|---------|-----------------------------|----------------------------|---------|
| | LXRF/PbB | LXRF/EP | LXRF/CaNa ₂ EDTA | PbB/CaNa ₂ EDTA | PbB/EP |
| <i>r</i> | 0.388 | 0.200 | 0.472 | 0.701 | 0.499 |
| <i>p</i> | < 0.003 | > 0.010 | < 0.001 | < 0.001 | < 0.001 |

Correlation coefficients other than the correlation between LXRF and EP were statistically significant (Table 4) (13,14). Discriminant function analysis was carried out by entering corrected LXRF counts, PbB, EP, and age in a stepwise manner with the CaNa₂EDTA test result as the categorical criterion variable. Based upon this analysis, 90% of lead-toxic children were predicted correctly as being CaNa₂EDTA-positive or CaNa₂EDTA-negative. Neither age nor EP contributed to the power of the discriminant analysis. In a retrospective analysis of 59 similar lead-toxic children from our clinic using the indices of EP and PbB to predict CaNa₂EDTA outcomes, 78% of children were correctly categorized. Hence, by including bone lead measurements by LXRF, which has a high discriminant power alone, an additional 190,000 to 650,000 lead-toxic children in the U.S. could be correctly categorized and appropriately managed medically. By using net corrected LXRF counts and PbB values to predict CaNa₂EDTA outcomes, the specificity and sensitivity of these two

predictors were 86 and 93%, respectively (Table 5) (13,14). In 20 and 24% of CaNa₂EDTA-negative and CaNa₂EDTA-positive children, respectively, cortical bone lead values were similar to lead concentrations measured in bone biopsies from normal adults (17,18). Remarkably, an additional 40% of CaNa₂EDTA-positive children had bone lead concentrations observed in industrially exposed adults (17,18).

In this longitudinal study, lead-toxic children who did not qualify for treatment and other children who underwent one or two courses of CaNa₂EDTA 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 CaNa₂EDTA-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 (19–22). 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).

Table 5. CaNa₂EDTA test outcomes compared to predicted outcomes from a discriminant analysis using corrected LXRF photon counts and PbB values as independent variables (13,14).^a

| Actual CaNa ₂ EDTA test results | Predicted CaNa ₂ EDTA outcomes | |
|--|---|----|
| | + | - |
| + | 28 | 2 |
| - | 4 | 25 |

^a By using net corrected LXRF photon counts and PbB to predict CaNa₂EDTA test outcomes, the specificity [true negative (-) (n = 25)/true negative (-) plus false positive (+) (n = 29)] was 86% and the sensitivity [true positive (+) (n = 28)/true positive (+) plus false negative (-) (n = 30)] was 93%.

Discussion

The development and clinical validation of K-line XRF instruments in industrially exposed adults (23–24) and the L-line XRF technique in lead-toxic children

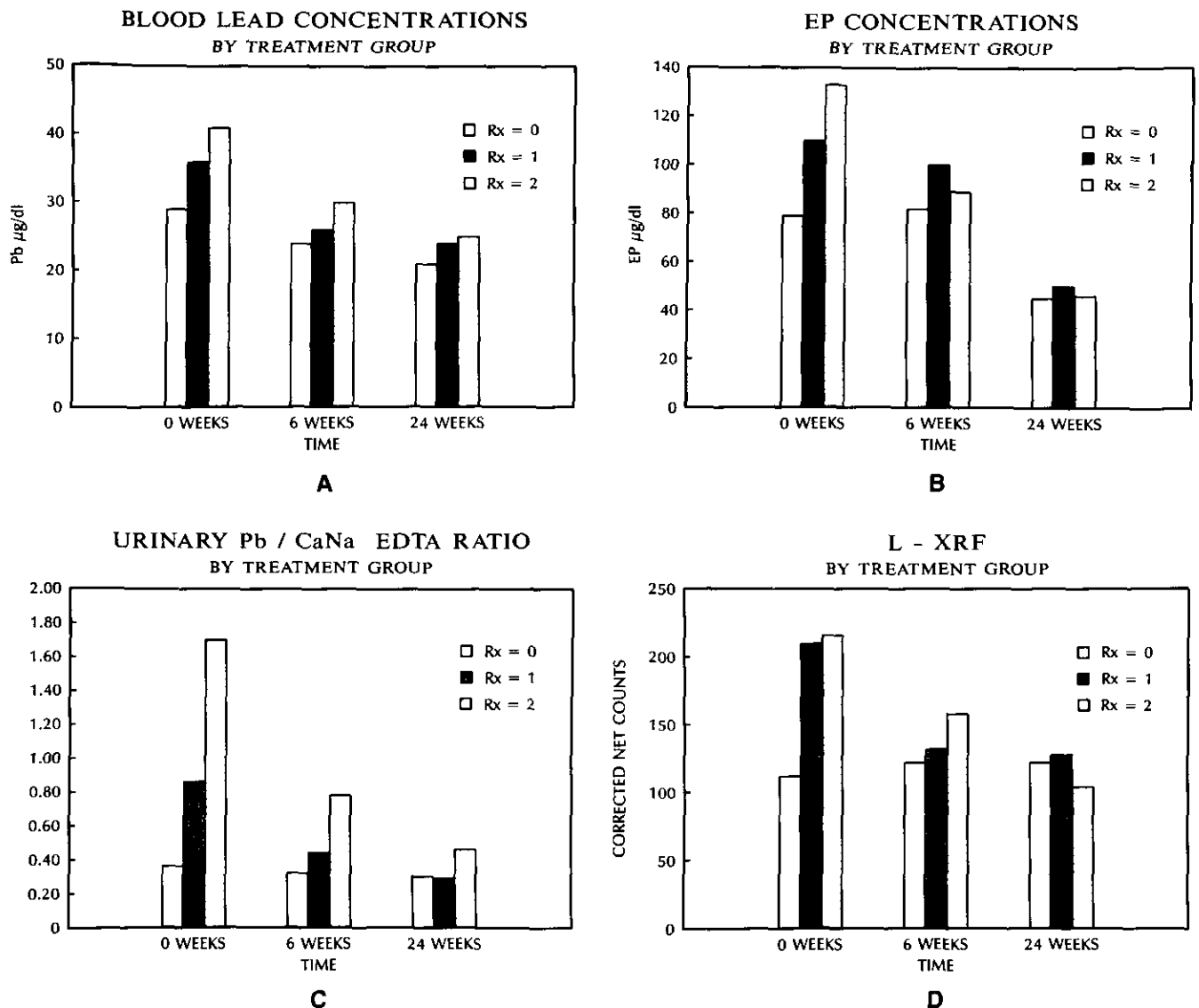


FIGURE 2. Sequential values for (A) PbB, (B) EP, (C) PbU/EDTA ratios, and (D) net corrected LXRF counts are shown in children at enrollment and 6 weeks and 6 months after enrollment. Rx = 0 indicates lead-toxic children who did not qualify for CaNa_2EDTA treatment; Rx = 1 represents children treated with one in-hospital course of a CaNa_2EDTA after obtaining baseline values at enrollment; and Rx = 2 indicates lead-toxic children treated in the hospital with CaNa_2EDTA after baseline values were obtained at enrollment and again 6 weeks post-enrollment.

(13,14,15) open exciting and highly relevant time windows of several months to several years to assess the impact of large bone reservoirs of lead on human health. These two XRF approaches to measure lead in bone are likely to shed further understanding on the biological information obtained by measuring lead in whole blood (6). The LXRF technique also presents a possibility for resolving long-standing uncertainties concerning fetal exposure to lead in relation to maternal lead stores. Moreover, XRF techniques may explore epidemiological connections between hypertension (25) and osteoporosis (26).

It is clear from previous work that concentrations of lead in bone (long bones and tooth dentine) correlate closely with the presence of lead nephropathy in adults (27) and neurobehavioral and cognitive impairments in children (20,22,28) (Table 6). Furthermore, during non-steady-state conditions (growth, pregnancy, lactation, demineralization of the skeleton), it is reasonable to expect that the metabolism of lead in bone is related 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 tech-

Table 6. Cortical bone lead values in children.

| Reference | Subjects | Mean, ppm wet weight |
|----------------------|----------------------------|----------------------|
| Barry (19) | Normals | 3 |
| Winnecke (20) | Normals | 3-5 |
| Grandjean (21) | Normals | 3-5 |
| Needleman (29) | Lead poisoned | ~ 31 |
| Winnecke (22) | Smelter exposed | ~ 12 |
| Rosen et al. (13,14) | Lead toxic | |
| (by LXRF) | CaNa ₂ EDTA (-) | 14 |
| | CaNa ₂ EDTA (+) | 29 |

nique have been proven. A PbB determination and LXRF measurement were predictive of the need for in-hospital chelation therapy in 90% 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 the 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 38 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, tibial cortical bone lead concentrations remained three to five times higher than concentrations in compact tooth bone in normal European children (19-22) (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 child-bearing 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.

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