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L-line x-ray fluorescence of cortical bone lead compared with the $CaNa_2EDTA$ test in lead-toxic children: Public health implications

(environmental health)

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ABSTRACT **Mild to moderate lead toxicity (blood lead, 25–55 μg/dl) is a preventable pediatric illness affecting several million preschool children ("lead-toxic children") in the United States. In-hospital lead-chelation treatment is predicated upon a positive $CaNa_2EDTA$ test, which is difficult to perform and impractical in large populations. After the development of an L-line x-ray fluorescence technique (LXRF) that measures cortical bone lead content safely, rapidly, and noninvasively, this study was initiated in lead-toxic children to compare LXRF with the $CaNa_2EDTA$ test. Moreover, LXRF provided the opportunity to quantify bone lead content. From blood lead and LXRF alone, 90% of lead-toxic children were correctly classified as being $CaNa_2EDTA$-positive or -negative. In 76% of 59 lead-toxic children, bone lead values measured by LXRF were equal to or greater than those measured in normal and industrially exposed adults. These results indicate that LXRF may be capable of replacing the $CaNa_2EDTA$ test. When considered with the known neurotoxic effects on children of "low levels" of exposure to lead, these results also suggest that either an excessively narrow margin of safety or insufficient safety is provided by present U.S. guidelines, which classify an elevated blood lead concentration as 25 μg/dl or greater.**

Environmental Pb exposure is a continuing health hazard for American children (1). Pb toxicity, defined as a blood Pb concentration (BPb) ≥ 25 μg/dl with an erythrocyte protoporphyrin level (EP) ≥ 35 μg/dl (1), is the most common preventable pediatric illness in the United States (1–3). Data from a 1976–1980 national survey indicated that at least 1.5 million U.S. preschool children had BPb ≥ 25 μg/dl ("lead-toxic children") (2). Although gasoline lead emissions and the lead content of food have decreased significantly during the past decade, about 5 million preschool U.S. children in 1988 are still at risk for Pb toxicity (3) from all sources of Pb, including dust, food, gasoline, and water, and especially from leaded paint in old substandard housing (1–3).

Pb toxicity in asymptomatic children with modest elevations in BPb values (between 25 and 55 μg/dl) is characterized by impairments in the metabolic pathways of vitamin D (4), heme (5), and erythrocyte nucleotide (6). BPb in this range is also associated with an IQ loss of about 2–5 points and decrements in cognition (7–9). BPb values below 25 μg/dl are not inconsequential (1, 3–11): Pb effects on human vitamin D and heme metabolism are apparent at BPb values of 12 and 15–18 μg/dl, respectively (5, 12). BPb < 15 μg/dl has been linked to deficits in development of cognition (13, 14) and of stature (15). Long-term effects (particularly neurobehavioral, cognitive, and developmental) have been observed recently in studies of children with BPb levels lower than previously believed harmful.

Because substantive public health concerns are expressed at BPb ≤ 25 μg/dl, standard screening methods and diagnostic techniques, which cannot identify large populations of asymptomatic Pb-toxic children who may require in-hospital chelation therapy, limit progress toward effective screening and diagnosis (16, 17). A screen for Pb toxicity is carried out by measurement of EP in a capillary sample of whole blood (1). This technique is fast and convenient and also identifies children with iron deficiency. However, the capability of EP screening to detect elevated BPb levels of 25–55 μg/dl in asymptomatic children is inadequate: only about half of the Pb-toxic children have an abnormal EP concentration (17).

In pediatric practice, when the EP is elevated, a BPb measurement is carried out. Based upon the BPb, medical intervention is instituted (1, 10). However, the residence $t_{1/2}$ of Pb in blood is short and reflects recent exposure (18, 19). Moreover, BPb does not reflect Pb levels in important target tissues, such as the brain, or changes in tissue Pb levels that occur when exposure is modified (20–23). BPb represents a short-term index of dynamic processes that include intake, equilibration, exchange between body compartments, and tissue sequestration (16, 18, 19, 24).

In Pb-toxic children, the decision to proceed with in-hospital chelation therapy is based upon the positive result of the $CaNa_2EDTA$ provocative test (1, 10), which is the current reference method for assessing total body Pb (16, 24–26). $CaNa_2EDTA$ chelates Pb in the extracellular fluid, thereby removing Pb from blood, soft tissues, and bone (10, 25, 26). Pb accumulates in cortical bone and teeth over a lifetime, where Pb stores account for about 75% of total body Pb in normal children (27). The $CaNa_2EDTA$ test requires an injection and an 8- to 24-hr quantitative urine collection, which is virtually impossible to achieve in large numbers of young children.

The development of L-line x-ray fluorescence (LXRF) for measuring cortical bone Pb noninvasively could provide a safe, rapid, painless, and widely applicable diagnostic technique (57). The present study was undertaken to evaluate LXRF as a possible substitute for the $CaNa_2EDTA$ provocative test and to quantify Pb in the tibial cortical bones of mildly to moderately Pb-toxic children.

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Abbreviations: BPb, blood Pb concentration (μg/dl); EP, level of erythrocyte protoporphyrin in whole blood (μg/dl); UPb, urinary Pb excretion (μg); XRF, x-ray fluorescence; LXRF, L-line XRF.

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MATERIALS AND METHODS

Clinical Research Design. Asymptomatic and untreated Pb-toxic children, 1–6 years old, were eligible for study if BPb was 25–55 μg/dl with EP > 35 μg/dl (1). Sequentially identified Pb-toxic children were enrolled in this study as part of a larger clinical research program to assess longitudinally the biochemical, electrophysiological, and neurobehavioral outcomes of chelation treatment. Within 1 week after the BPb and EP were determined, LXRF was carried out about 45 min after sedation with chloral hydrate administered orally (25–100 mg/kg of body weight). One day later, an 8-hr $CaNa_2EDTA$ test was performed: (*i*) 500 mg of $CaNa_2EDTA$ per m^2 of body surface was administered i.v.; (*ii*) for the next 8 hr, all urine was collected in a lead-free apparatus (28, 29); (*iii*) the results of the 8-hr test were expressed as a ratio of the amount (μg) of Pb excreted divided by the amount (mg) of $CaNa_2EDTA$ administered (10). When this ratio was ≥ 0.60, the test was considered positive, and that child was admitted to the hospital for $CaNa_2EDTA$ therapy (10).

BPb, EP, and Urinary Pb Excretion (UPb) Measurements. BPb was measured by flameless atomic absorption spectroscopy (4, 12, 28, 29). EP was measured by extraction and fluorometry (4, 12, 28, 29). Our laboratory participates successfully in the proficiency testing program of the Centers for Disease Control. UPb was measured as reported elsewhere (28, 29).

LXRF Instrumentation and Parameters. The LXRF instrument comprises a low energy x-ray generator (Philips Electronics, Bristol, PA) with a silver anode, a Li-doped Si detector (EG & G Ortec, Oak Ridge, TN), a polarizer of incident photons, and a multichannel x-ray spectrum analyzer (Nuclear Data, Schaumburg, IL).‖ Partially polarized photons are directed at the subcutaneous, medial midtibial cortex. The LXRF spectrum, measured 90° from the incident beam, reveals a peak in the 10.5-keV region, which represents the Pb L_α line XRF. To correct for the attenuation of fluorescence photons by pretibial soft tissue, thickness measurements were carried out ultrasonically with a 7-MHz transducer. Pretibial soft-tissue thicknesses ranged from 3 to 8 mm (median, 5 mm).

The average surface skin dose, deliberately limited to 1 rad (0.01 Gy) over a 5-cm^2 area, was delivered in 16.5 min. The effective whole-body-equivalent radiation dose was calculated to be 2.5 μSv, about 1/20th that of one dental x-ray and about 1/10th to 1/25th that from one radiographic examination of the chest (30–33).** 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 (34). Hence, within the same population, LXRF measurements of the tibia are much less risky than those dental and pulmonary radiological examinations that are performed routinely.

The 16.5-min photon count was measured in the Pb L_α peak from the medial aspect of the tibia (with intact pretibial soft tissue) of each of nine amputation specimens. These measurements were compared to several atomic adsorption measurements of Pb in full cross sections of each tibial bare bone subjacent to the area of LXRF examination. Bone Pb analyses by atomic adsorption ranged from 9 to 49 μg of Pb per g of wet weight. For a tibia with an overlying skin thickness of 5 mm, each additional 1 μg of Pb per g of tibial cortical bone above the minimum detection limit added an average of 14 net Pb L_α line fluorescence photon counts during a 16.5-min assay time. For this skin thickness, the minimum detection limit was estimated to be 7 μg of Pb per g. A detailed study of the physics

‖Wielopolski, L., Slatkin, D. N. & Rosen, J. F., U.S. Patent Application 07/158,495, Feb. 22, 1988.

**Lithium fluoride dosimeters were used to determine the radiological risk assessment. These data are available from the authors upon request (report from J.A.K.-E. to J.F.R., Sept. 30, 1986).

Table 1. Clinical research data in 59 Pb-toxic children

ID	Age, mo	BPb, μg/dl	EP, μg/dl	UPb/ $CaNa_2EDTA$ ratio	Skin thickness, mm	Corrected LXRF counts
			$CaNa_2EDTA$-negative patients			
90	20	26	70	0.12	7	176
77	18	30	41	0.14	7	19
80	35	33	99	0.23	7	73
70	25	34	87	0.23	6	160
83	47	30	55	0.24	5	14
98	36	29	98	0.26	5	83
62	24	22	53	0.27	6	199
43	34	29	111	0.30	5	32
88	14	28	57	0.31	7	112
55	49	24	78	0.33	4	119
34	30	27	42	0.34	6	52
40	28	44	180	0.35	5	25
17	42	28	46	0.36	6	86
36	28	31	82	0.38	6	91
59	44	26	39	0.39	5	86
92	36	26	56	0.39	5	191
78	59	34	64	0.41	5	158
42	48	27	80	0.42	6	73
69	21	28	71	0.42	7	168
26	20	31	78	0.47	6	132
16	62	24	32	0.48	4	54
89	28	36	163	0.48	5	86
38	31	31	84	0.50	5	196
33	23	31	82	0.51	6	39
27	27	26	125	0.51	7	103
63	20	37	144	0.57	6	146
60	48	34	183	0.58	6	97
61	37	25	115	0.58	5	129
35	33	23	58	0.58	4	185
71	35	38	183	0.59	6	156
			$CaNa_2EDTA$-positive patients			
73	58	27	28	0.60	5	256
82	13	34	106	0.60	8	432
67	24	36	71	0.61	5	233
64	52	40	83	0.62	4	186
41	34	43	163	0.65	5	214
37	53	29	118	0.66	5	354
58	56	27	152	0.73	5	163
72	34	45	110	0.74	5	288
85	58	42	99	0.76	4	280
87	16	38	76	0.77	6	157
94	37	30	219	0.79	3	96
53	20	25	72	0.82	4	182
79	50	36	317	0.82	8	232
30	15	41	88	0.89	7	166
25	31	37	87	0.92	7	199
15	54	36	124	0.96	4	103
29	49	35	44	0.98	6	161
44	31	46	84	0.99	6	84
74	59	49	77	1.02	6	273
31	34	25	84	1.03	5	150
84	29	44	128	1.14	5	480
95	63	47	169	1.17	3	412
52	33	39	133	1.19	6	136
22	61	40	87	1.21	4	250
97	52	46	250	1.26	4	198
54	21	52	214	1.28	7	206
57	80	45	70	1.30	4	147
28	49	43	151	1.39	3	169
50	29	53	218	1.64	7	259

ID, patient identification number; mo, months.

Table 2. BPb, EP, UPb, and net corrected LXRF values in Pb-toxic children

$CaNa_2EDTA$ test result	Age, mo	BPb, μg/dl	EP, μg/dl	Ratio of UPb/$CaNa_2EDTA$	Corrected LXRF values: Photon counts	Corrected LXRF values: Bone Pb,* μg of Pb per g
Negative (n = 30)	33 ± 10	30 ± 5	89 ± 43	0.39 ± 0.13	106 ± 56	12 ± 2 (range, 7–52)
Positive (n = 29)	38 ± 15†	39 ± 8†	125 ± 65‡	0.95 ± 0.27‡	223 ± 96†	37 ± 3‡ (range, 7–200)

Values are means ± SD.
*Normal adult values for tibial Pb are 19–27 μg of Pb per g (36, 37). Values for tibial Pb in adult workers in lead industries are ≥ 30 μg of Pb per g (36, 37).
†$P < 0.05$ vs. $CaNa_2EDTA$-negative group.
‡$P < 0.01$ vs. $CaNa_2EDTA$-negative group.

and calibration of this LXRF instrumentation will be reported elsewhere (57).

The net XRF photon count for each child was corrected according to the day-to-day reproducibility of the XRF instrument by repeated measurements of a bone phantom containing 8 μg Pb per g of bone. The day-to-day reproducibility (within 18 months) of the LXRF measurement was ±5.1% (95% confidence interval). To assess the reproducibility of LXRF examinations, 26 of the 59 Pb-toxic children in this study underwent a second LXRF measurement of the anteromedial surface of the tibia after repositioning of the instrument 5 cm distal from the first examination. The reproducibility of repeated LXRF measurements at different locations was ±9.2% (95% confidence interval).

Soft-Tissue Absorption of x-Rays. Pb L x-rays and x-rays used to excite them are readily absorbed by soft tissue. To quantify x-ray attenuation, the net 16.5-min photon count in the Pb 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. Similar results were obtained from regression analysis of these ratios with respect to soft-tissue thickness (57).

Quantification of Bone Pb Concentrations. The average concentration of Pb in the full cross section of tibial bone subajacent to the area of LXRF examination was measured by several flameless atomic adsorption measurements (Varian Spectra 30P with GTA 95) of dissolved bone from each of the nine amputated specimens. The average value of the ratio of the tibial bone concentration (μg/g) to the net corrected LXRF photon count, normalized to the median soft-tissue thickness of 5 mm, was 0.09 ± 0.01 (mean ± SEM).

Statistics. Pearson product moment correlations and stepwise discriminant function analysis with the Wilk's λ criterion were used (35).

RESULTS

Based on objective assessments of the quality of housing of these Bronx children, on their ages, and on the distribution of their BPb, EP and UPb/$CaNa_2EDTA$ values (Tables 1 and 2), these 59 Pb-toxic children were representative of the majority of children attending Pb-toxicity programs nationally (1, 3, 10, 24, 28, 29). $CaNa_2EDTA$-positive children compared with $CaNa_2EDTA$-negative children had higher BPb and EP as well as high net corrected LXRF photon counts (Tables 1 and 2). Correlation coefficients were statistically significant other than the correlation between LXRF counts and EP (Table 3).

Discriminant function analysis was carried out by entering LXRF counts, BPb, EP, and age in a step-wise manner with the $CaNa_2EDTA$ test result as the categorical criterion variable (35). BPb and net corrected LXRF counts in 59 children contributed almost equally to the standardized discriminant function coefficients (Table 4). Neither EP nor age contributed to the final discriminant function.

Based upon this analysis, which included BPb and net corrected LXRF counts as predictors, 90% of the Pb-toxic children were correctly classified as being $CaNa_2EDTA$-positive or -negative. The specificity and sensitivity of these two predictors were 86% and 93%, respectively (Table 5).

Bone Pb concentrations were calculated for each child, after its Pb L_α signal was converted to that which would have been observed with a skin thickness of 5 mm (Table 2). The bone Pb content in $CaNa_2EDTA$-positive patients was 2- to 3-fold greater than that in $CaNa_2EDTA$-negative children (Table 2). In 23% and 28% of $CaNa_2EDTA$-negative and -positive children, respectively, cortical bone Pb was equal to or greater than Pb measured in bone biopsies from normal adults (36, 37). Remarkably, an additional 48% of $CaNa_2EDTA$-positive children had bone Pb concentrations observed in industrially exposed adults (36, 37).

DISCUSSION

An LXRF measurement of cortical bone Pb with a BPb measurement was correctly predictive of the $CaNa_2EDTA$ test outcome in 90% of 59 untreated Pb-toxic children. This low-energy LXRF instrument was designed with an essentially confined radiation system. Thus, a parent can be present during the LXRF measurement with negligible risk from scattered radiation. Therefore, LXRF may prove to be suitable for assessing large numbers of Pb-toxic children to select objectively those patients who require in-hospital chelation therapy. We estimate that one such instrument can examine about 3500–5000 children per year. As further improvements in the detector and polarizer are made, the minimum detection limit and photon-counting time are anticipated to be decreased several fold. Furthermore, if the Sr/Ca mass ratio in the bones of U.S. preschool children

Table 3. Statistical analyses of net corrected LXRF photon counts, BPb, EP, and $CaNa_2EDTA$ test results from 59 Pb-toxic children

Pearson correlation coefficients	Analysis of tests: LXRF/BPb	LXRF/EP	LXRF/$CaNa_2EDTA$	BPb/$CaNa_2EDTA$	BPb/EP
r	0.388	0.200	0.472	0.701	0.499
P	<0.003	>0.10	<0.001	<0.001	<0.001

Table 4. Discriminant function analysis

Initial discrimination			Final discriminant function coefficient	
Variable	Wilk's λ	Significance	Standardized	Unstandardized
LXRF	0.649	<0.001	0.693	0.0087
BPb	0.658	<0.001	0.678	0.104
EP	0.902	<0.016	—	—

Net corrected LXRF, BPb, and EP were entered stepwise in discriminant function analysis. The discriminant function score is calculated for each Pb-toxic child by using the equation: −5.0061 +0.0087 (LXRF) +0.104 (BPb). A large Wilk's λ, such as the one for EP, indicates a weak discrimination.

varies as little as it does in Japan (mean ± S.D., 310 ± 30 μg of Sr per mg of Ca; ages 1–6 years) (38), it is likely that the usefulness of LXRF can be expanded by measuring L-line Pb/K-line Sr signal ratios from the 10–16 keV interval of the XRF. In contrast, the $CaNa_2EDTA$ test requires prolonged, quantitative urine collections, which are difficult to achieve in a young child. In our own clinic, two nurses can supervise no more than 250–300 such tests per year. For these reasons, we suggest that it may be more appropriate to perform an LXRF test rather than a $CaNa_2EDTA$ test to categorize children for chelation therapy.

A low but statistically significant correlation between BPb and LXRF photon counts was found (Table 3); similarly low correlations between BPb and LXRF photon counts have been observed in adults (39, 40). We surmise that BPb measurements alone may not adequately reflect the magnitude of the body burden of Pb in mildly to moderately Pb-toxic children.

The potential advantages and limitations of this instrument are seen from this circumscribed study of 59 Pb-toxic children. LXRF and BPb measurements contributed almost equally to the power of the discriminant analysis. BPb measurements alone indicated that 80% of Pb-toxic children could be correctly classified; and LXRF analysis alone correctly predicted the $CaNa_2EDTA$ outcome in 76% of Pb-toxic children. If BPb or LXRF were used alone as the predictor of the $CaNa_2EDTA$ outcome, the proportion of false-positive results would increase from 6% to 13%; and the proportion of false-negative results would increase from 13% to 24%. Moreover, in a retrospective analysis of 59 similar Pb-toxic children from our clinic using the conventional indices of EP and BPb to predict $CaNa_2EDTA$ outcomes, 78% of children were correctly classified, rather than 90% that would have been correctly categorized by LXRF and BPb measurements. Therefore, by including bone Pb measurements by LXRF, which has a high discriminant power alone, at least an additional 190,000 to 650,000 Pb-toxic children in the U.S. could be correctly categorized and appropriately managed medically (1–3).

Table 5. $CaNa_2EDTA$ test outcomes compared to predicted outcomes from a discriminant analysis using corrected LXRF photon counts and BPb values as independent variables

		Predicted $CaNa_2EDTA$ outcomes	
		+	−
Actual $CaNa_2EDTA$ test results	+	28	2
	−	4	25

By using net corrected LXRF photon counts and BPb to predict $CaNa_2EDTA$ test outcome, 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%.

Our data (Table 3) indicate an (r) value of 0.472 ($P < 0.001$) between LXRF and $CaNa_2EDTA$ results. To our knowledge, these are the only such data available. In Pb-poisoned adult workers, correlation coefficients between L-line and K-line XRF and $CaNa_2EDTA$ results varied from 0.50 and 0.79 (41–43). LXRF directly measures Pb in cortical bone, whereas the $CaNa_2EDTA$ test provides an indirect measure of Pb in the extracellular fluid of soft and hard tissues (10, 25, 26). Children retain a far greater fraction of absorbed Pb than do adults (44). This high degree of Pb retention in children may also explain the lower (r) value observed between LXRF and $CaNa_2EDTA$ results.

A skeletal subcompartment of bone Pb is readily exchangeable (18, 19, 24, 45–50) and contributes to perturbations in essential metabolic pathways together with on-going exposure from other external sources (24). Hence, the markedly elevated content of Pb in cortical bones of Pb-toxic children has serious public health implications (13, 14, 18, 19, 24, 45–50).

Cortical bone or tooth Pb values reported in normal European children ranged from 1.4 to 12.7 μg of Pb per g (mean, 4.7 μg of Pb per g) (9, 27, 51, 52). In European children living near a smelter, the range in tooth Pb was from 1.9 to 38.5 μg of Pb per g (mean, 6.16 μg of Pb per g) (51). In contrast, when leaded paint was at least as widespread in the United States as it is now (1) and when leaded gasoline was more widely used, whole-tooth Pb concentrations in Philadelphia children were about 10–85 μg of Pb per g (53). In contrast to bone Pb in Pb-toxic children (Table 2), ancient Peruvian adult bones contained about 0.04 μg of Pb per g (dry weight) (54, 55). Our data indicate that bone Pb concentrations in Pb-toxic children are about 1200 to 3700 times greater than those in ancient Peruvian bones (54–56). Furthermore, cortical bone Pb values in moderately lead-toxic children < 7 years old, in many instances, now are equivalent to bone Pb concentrations observed in normal adults and in lead workers (36, 37). BPb values currently accepted as mildly or moderately elevated are actually associated with a strikingly high Pb burden (54–56), with distinct toxic effects on children (13, 14, 18, 19, 24, 45–50).

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