Pathology (December 2012) **44(7)**, pp. 626–631

CHEMICAL PATHOLOGY

Cadmium and lead in Hong Kong school children

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Summary

Aim: Cadmium (Cd) and lead (Pb) are toxic elements in our environment. This study is to determine the reference intervals of Cd and Pb in blood and urine from Hong Kong school children and to identify their determinants.

Methods: A total of 2209 secondary school children and 893 preschool children were recruited. Cd and Pb in blood and urine were measured by inductively-coupled plasma mass spectrometry.

Results: Blood Cd was affected by age, smoking and residential district, while urine Cd was influenced by age and blood Cd. Blood Cd was positively correlated with smoking as confirmed by urinary cotinine (rho = 0.183, $p < 0.001$, $n = 2074$). Blood Pb was dependent on gender and residential district, while urinary Pb was dependent on gender and blood Pb. Students from schools of lower academic grading had higher blood Cd and Pb than those from higher academic grading schools ($p < 0.001$, respectively). Urinary albumin was positively associated with urinary Cd and Pb.

Conclusions: Using a non-occupationally exposed population, the reference ranges are: blood Cd <21.9 nmol/L for smokers and <8.8 nmol/L for non-smokers, and blood Pb <203.8 nmol/L. Reference intervals for urinary Cd and Pb are also reported.

Key words: Cadmium, Chinese, inductively-coupled plasma, lead, mass spectrometry, reference interval.

Received 29 October 2011, revised 20 April, accepted 6 May 2012

INTRODUCTION

There has been an increasing number of locally reported cases[1,2] of heavy metal poisoning due to worsening environmental pollution or contamination,[3] and heightened alertness of the lay public and medical practitioners by repeated warnings from overseas and local health authorities in recent years.[4,5] Heavy metal poisoning can be associated with accidental over-exposure from dietary,[6] industrial,[7] drug-related,[1] or even cosmetics-related[8] sources. Signs and symptoms of heavy metal poisoning are usually subtle and not well defined because the effect of heavy metal toxicity can vary from gastrointestinal upset to severe neurological damage. Due to the difficulty in clinical diagnosis, laboratory screening for heavy metals is commonly requested for the diagnostic work-up of patients suspected of poisoning. However, the debate on 'how toxic is toxic' remains a rather philosophical question. The Centers for Disease Control and Prevention (CDC) USA published a detailed report on human exposure to environmental chemicals in 2005.[9] The main purpose of the CDC report is to provide unique exposure information to scientists, physicians, and health officials to help prevent disease that results from exposure to these environmental chemicals. However, population-based references for heavy metals are lacking in Hong Kong. Such data are important to facilitate the accurate interpretation of heavy metal screening. The objectives of this study were to determine the population-based reference intervals for lead (Pb) and cadmium (Cd) in blood and urine samples using inductively-coupled plasma mass spectrometry (ICP-MS) technique which is capable of simultaneous analysis of multiple elements. This study also analysed the relationship between these two heavy metals and various clinical parameters in Hong Kong children.

MATERIALS AND METHODS

Subjects

Healthy non-occupationally exposed (to heavy metals) secondary school children and young adults were randomly recruited from various districts of Hong Kong. Details of the study methodology have been previously described.[10,11] The socio-demographic and clinical data including sex, age, smoking and dietary habits, fat distribution, systolic and diastolic blood pressures, pulse rate, waist and hip circumferences, body weight and height for calculation of body mass index (BMI) were collected. Liver and renal function tests, fasting plasma glucose, full lipid profile, and urine cotinine and trace elements and heavy metals were measured. Another group of subjects were recruited from randomly selected local nurseries and kindergartens. A random spot urine specimen was collected for the measurement of creatinine, cadmium and lead. Whole blood was collected into EDTA tubes free of cadmium and lead. Urine samples were collected into acid-washed bottles certified for the analysis of trace elements and heavy metals in urine matrices. All samples were stored at −70°C until analysis.

Biochemical assays

Urine creatinine was measured by the modified version of Jaffe reaction and urinary albumin was measured by immunoturbidimetric assay (DP Modular Analytics; Roche Diagnostics, USA). Urine cotinine was measured by chemiluminescent immunoassay (Immulite 1000 analyser; Siemens Healthcare Diagnostics, USA). EDTA blood samples were used for assessment of complete blood picture including red cell parameters (GEN-S blood cell counter; Beckman-Coulter, USA). Lead and cadmium in blood and urine were assayed by inductively-coupled plasma mass spectrometry (ICP-MS 7500c; Agilent

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: 10.1097/PAT.0b013e328359cfe7

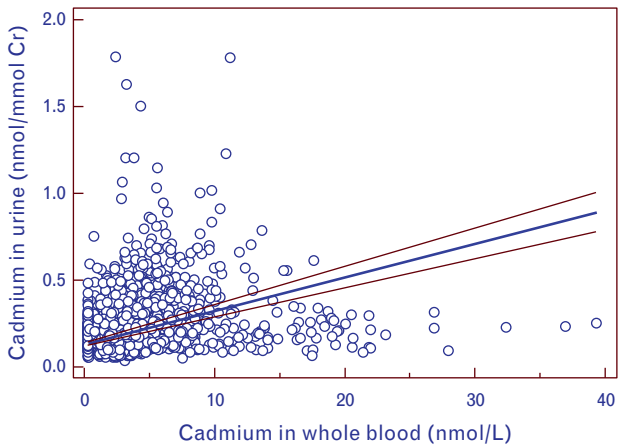

Fig. 1 Relationship between urine Cd and blood Cd ($y = 0.01938\ x + 0.1289$; $n = 2042$; $r = 0.329$; $p < 0.001$). The two red lines are 95% confidence intervals.

Technologies, USA). Briefly, samples were pre-treated with a diluent containing 0.05% tetra-methyl ammonium hydroxide and a mixture of internal standards containing rhodium, yttrium and iridium before analysis. Sample aerosol generated by a neubiliser was carried to an argon plasma of about 8000 K for the production of elemental ions. The sample ions were then introduced into a mass spectrometer for ion identification and quantification. The inter-assay coefficients of variation were <6%. The detection limits were 1.0 nmol/L for Pb in urine and blood, 0.27 nmol/L for blood Cd and 0.30 nmol/L for urinary Cd.

Statistical analysis

The Kolmogorov–Smirnov test was used to test the data distribution for normality. Data analysis for Spearman's coefficient of rank correlation (rho), Mann–Whitney U test and Kruskal–Wallis test were computed using the MedCalc 7.0 program (http://www.medcalc.be). The concentrations of Cd and Pb in blood and urine were logarithm-transformed to normal distribution for calculation of geometric means. Correlation coefficient (r) was performed by SPSS 17.0 (SPSS, USA). Righted-sided 95% confidence intervals were chosen as reference ranges for Pb and Cd as they are toxic in high levels. *p*-values less than 0.05 were considered significant.

RESULTS

A total of 2209 and 893 subjects were recruited from 14 secondary schools and 21 nurseries and kindergartens, respectively. The age range was 1–21 years and 48.5% were male. Blood Cd was affected by age, smoking and residential district, while urine Cd was influenced by age and blood Cd. Blood Cd was positively correlated with urinary Cd ($rho = 0.329$, $p < 0.001$, $n = 2042$; Fig. 1). Blood Cd but not urinary Cd was positively correlated with smoking habit as confirmed by measurable urinary cotinine ($rho = 0.183$, $p < 0.001$, $n = 2063$). Smoking subjects had a higher median level of blood Cd than non-smoking subjects (6.12 versus 3.23 nmol/L; $p < 0.001$; Table 1). Blood Pb was dependent on gender and residential district, while urinary Pb was dependent on gender and blood Pb. Blood Pb was positively correlated with urinary Pb ($rho = 0.208$, $p < 0.001$, $n = 2036$; Fig. 2). Males have a higher median concentration of blood Pb than females (132.9 versus 105.1 nmol/L; $p < 0.001$), while urinary Pb was higher in females than in males (median 0.50 versus 0.44 nmol/mmol Cr). Significantly lower levels of Cd and Pb in both blood and urine samples were found in students living in Hong Kong Island than in Kowloon or the New Territories ($p < 0.001$ for both; Table 1). Students from schools of lower academic grading (Band 3) had higher blood Cd and Pb levels than those of higher academic grading (Band 1 and 2) ($p < 0.001$, respectively).

Population reference ranges using ICP-MS

In this normal, non-occupationally exposed population, the local reference ranges (right-sided 95% reference interval) for Cd in blood were <21.9 nmol/L for smokers (Table 2, $n = 90$) and <8.8 nmol/L for non-smokers ($n = 1984$), and that for blood Pb was <203.8 nmol/L ($n = 2209$). Reference intervals according to different age groups for urinary Cd and Pb with/without correction for urine creatinine are shown in Table 3. There was no significant difference in urinary Cd between smoking and non-smoking subjects.

Heavy metals and the haematopoietic system

Blood Pb was positively correlated with red blood cell number ($r = 0.104$, $p < 0.001$) and red cell distribution width (RDW; $r = 0.120$, $p < 0.001$), and inversely correlated with mean cell volume (MCV; $r = -0.125$, $p < 0.001$) and mean cell haemoglobin concentration (MCHC; $r = -0.116$, $p < 0.001$) after controlling for age and gender.

Table 1 Concentrations of cadmium and lead according to the description of sample individuals

Analyte	No. of subjects	Blood cadmium (nmol/L)	Urine cadmium (nmol/mmol Cr)	Blood lead (nmol/L)	Urine lead (nmol/mmol Cr)
Smoking					
Yes	90	6.12 (21.87)*	0.19 (0.58)	123.0 (197.0)	0.34 (0.86)
No	1984	3.23 (8.81)	0.20 (0.53)	117.9 (199.5)	0.42 (1.13)
p value†		<0.001	0.596	0.101	0.010
Residential district					
Hong Kong Island	368	2.41 (6.90)	0.18 (0.41)	104.9 (167.6)	0.38 (0.82)
Kowloon	457	3.56 (13.51)	0.19 (0.51)	111.4 (195.6)	0.40 (1.09)
New Territories	1384	3.55 (8.87)	0.20 (0.55)	123.6 (214.1)	0.43 (1.12)
p value‡		<0.001	<0.001	<0.001	<0.001
Academic grading of school					
Band 1	991	3.17 (8.80)	0.19 (0.51)	108.1 (190.9)	0.41 (1.05)
Band 2	474	3.22 (8.25)	0.19 (0.49)	119.4 (201.1)	0.38 (0.86)
Band 3	744	3.57 (9.88)	0.20 (0.55)	129.9 (221.1)	0.44 (1.09)
p value‡		<0.001	0.002	<0.001	<0.001

* Expressed as median (95% reference interval, right-sided).
† Compared by Mann–Whitney U test.
‡ Compared by Kruskal–Wallis test.

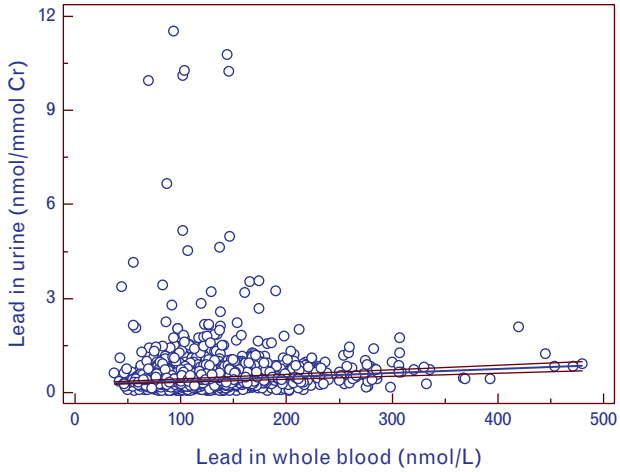

Fig. 2 Relationship between urine Pb and blood Pb ($y = 0.001212\ x + 0.2619$; $n = 2036$; $r = 0.208$; $p < 0.001$). The two red lines are 95% confidence intervals.

Heavy metals and albuminuria

Urinary albumin was positively correlated with urinary Cd (rho = 0.119, $p < 0.001$, Table 4) and Pb (rho = 0.150, $p < 0.001$). Albuminuria was defined as urine albumin-creatinine ratio >3.5 mg/mmol. However, there was no significant difference between normal ($n = 1909$) and albuminuric subjects ($n = 151$) for both Cd and Pb.

DISCUSSION

Cadmium and Pb are trace elements present in the environment with no known biological role in humans.[12,13] Cd is a by-product of zinc and lead smelting. It is used in electroplating, production of nickel-based rechargeable batteries, as a common pigment in organic-based paints and in tobacco products. Breathing the fumes of Cd vapours leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. A common source of chronic exposure is spray painting of organic-based paints without the use of a protective breathing apparatus. Non-industrial sources of exposure are cigarette smoke and food (from contaminated soil and water). Environmental exposure to Pb has decreased considerably in countries that have banned leaded gasoline, but it is still a major environmental health problem in countries that continue to use leaded gasoline, or where people are exposed to deteriorated residential lead-based paint or lead glazed ceramics used for storage and preparation of food.[14]

The kidney is the main organ affected by chronic Cd toxicity as it is a major route of excretion. Chronic exposure to Cd causes renal damage.[15] Renal dysfunction with proteinuria of slow onset (over a period of years) is the typical presentation. Cd accumulates in the kidney due to its preferential uptake by receptor-mediated endocytosis of freely filtered and metallothionein bound Cd (Cd-MT) in renal proximal tubule.[16] Internalised Cd-MT is degraded in endosomes and lysosomes, releasing free Cd(2+) into the cytosol, where it can generate reactive oxygen species (ROS) and activate cell death pathways. An early and sensitive manifestation of chronic Cd renal toxicity is impaired reabsorption of low molecular weight proteins (LMWP) such as retinol binding protein (RBP) causing tubular proteinuria and this is a good index of proximal tubular damage. Continued and heavy Cd exposure can progress to clinical renal Fanconi's syndrome, and ultimately to renal failure. In this study, urinary Cd and Pb were positively correlated with albuminuria. This finding suggests that heavy metals cause renal damage in our normal populations; however, the associations were weak as N-acetyl-β-D-glucosaminidase and β2-microglobulin are more sensitive markers for tubular damage in environmental exposure of Cd.[17,18]

In this non-occupationally exposed childhood population, normal blood Cd concentration was <8.8 nmol/L and most readings were in the interquartile range (IQR) of 2.29–4.50 nmol/L. Significantly increased blood Cd <21.9 nmol/L (reference interval, right-sided) was associated with tobacco use.[19] Smoking is a source of Cd exposure in the general population;[20] however, no significant difference was found in urinary Cd between smokers and non-smokers. The biological half-life of Cd in blood is 2–3 months.[21] These findings support the idea that blood Cd may reflect more recent exposure to Cd compared to urine Cd levels.[22] Besides, our subjects may only smoke occasionally. In other population-based studies, the reference values for Cd were <2.67 nmol/L in blood and <1.78 nmol/L in urine for German non-smokers.[23] Blood Cd levels in our subjects were similar to or lower than those reported in other countries (Table 5) and urine Cd levels were higher than the Germans (Table 6). In our study, urine Cd was positively correlated with blood Cd, suggesting that blood and urine Cd are useful markers for Cd exposure in the environment that link recent and chronic Cd exposure. Diet is known to be a major source of Cd exposure in the non-smoking general population. Blood Cd mainly reflects recent exposure and urine Cd increases in proportion to the amount of Cd stored in the body.[14]

Contamination during sample collection and measurement is an issue for trace elements analysis. In our study, we found that

Table 2 Concentrations of cadmium and lead in blood samples

Analyte	Blood cadmium (nmol/L)		Blood lead (nmol/L)
Smoking	Yes	No	–
Range	<0.27–39.27	<0.27–36.94	37.51–480.1
Median	6.12	3.23	117.3
Geometric mean	6.41	3.02	118.0
95% reference interval, right-sided*			
All	21.87 (90)	8.81 (1984)	203.8 (2209)
11–15 years	NA (33)	8.64 (1022)	208.8 (1140)
16–21 years	NA (57)	8.87 (962)	198.4 (1069)

* Expressed as 95% reference interval, right-sided (number of students).
NA, not available as the sample size was too small for reference interval determination.

Table 3 Concentrations of cadmium and lead in urine samples.

Analyte	No. subjects	Urine cadmium (nmol/L)	Urine cadmium (nmol/mmol Cr)	Urine lead (nmol/L)	Urine lead (nmol/mmol Cr)
Range		<0.30–29.26	<0.03–1.38	<1.00–177	<0.04–7.66
Median		1.73	0.22	3.93	0.47
Geometric mean		1.68	0.22	3.61	0.48
95% reference interval, right-sided					
All	3102	6.55	0.55	11.74	1.45
1–5 years	700	2.97	0.59	9.19	2.01
6–10 years	193	3.58	0.62	9.43	1.59
11–15 years	1136	6.73	0.47	13.23	1.13
16–21 years	1073	7.89	0.57	12.20	1.13

there were four urine samples with the highest Cd concentration but their paired blood samples had low Cd levels; there were six urine samples with the highest Pb concentration but with low blood Pb levels. These may be due to contamination during sample collection or analysis and they were excluded from further data analysis.

In this study, normal blood Pb concentration was <203.8 nmol/L and most readings were in the IQR of 94.6–146.0 nmol/L. Significantly lower urinary Pb levels were found in smokers than in non-smokers. Such significance disappeared when adjusted for subjects' age, implying that there was no difference in urinary Pb between smokers and non-smokers in our study. Our reference interval for blood Pb was higher than that of Germany (<168.9 nmol/L). The geometric mean exposure of blood Pb in Hong Kong was higher than that of occupationally non-exposed citizens in northern Germany and New York but lower than in China and Japan (Table 5). However, the level of urinary Pb in Hong Kong school children is similar to children from Germany but lower than Korean children.[24] Their Cd and Pb concentrations were determined by graphite furnace atomic absorption spectrometry (GFAAS), which is prone to interference and the accuracy is lower when compared to ICPMS. Comparison study showed that ICP-MS results were slightly lower than those from GFAAS.[25] Taking this into account, Korean children still had higher exposure to Cd and Pb than Hong Kong children.

Chronic Pb exposure can adversely affect central nervous, renal, cardiovascular, reproductive and haematological systems.[14] Lead readily passes through the placenta, and the central nervous system is particularly vulnerable to Pb toxicity during early development.[26] The threshold of Pb poisoning in children set by CDC is 100 μg/L, which is equivalent to 483 nmol/L. Cross-sectional and prospective epidemiological studies have shown impairment of cognitive and behavioural development in children at or below blood Pb levels of 100 μg/L. From our study, students from schools of lower academic grading had higher concentrations of blood Pb. This finding implied that chronic exposure to high blood Pb might affect students' academic performance. Considerable efforts have been spent in measuring the cognitive effects of Pb exposure at levels below those leading to overt signs of encephalopathy.[27–30] CDC reiterates a key message in the 2004 Morbidity Mortality Weekly Review (MMWR)[31] that there is no safe blood Pb level and all sources of Pb exposure for children should be eliminated.

Consistent with other authors,[32,33] we observed higher blood Pb levels among males than females. This finding might be explained by higher Pb exposure in men or that Pb bound to erythrocytes in the circulation[34] and men have higher haematocrit levels. The half-life of Pb in blood approximates that of erythrocytes (~35 days), whereas it is about 2 years in the brain and 10 years in bone.[14]

Lead is known to be toxic for the haematopoietic system.[14] Pb inhibits heme-synthetic enzymes including 5-aminolevulinic acid (ALA) synthase, ALA dehydratase, ferrochelatase and coproporphyrinogen decarboxylase, leading to lower haemoglobin synthesis. In this study, we observed a trend for an inverse correlation between haemoglobin and blood Pb levels. On the other hand, blood Pb levels were found to be inversely correlated with MCV and MCHC. Besides, blood Pb increased with increasing RBC number and RDW. This is because Pb decreases RBC survival and increases RBC production, resulting in more immature RBC in the circulation.

Hong Kong is geographically close to the Pearl River Delta (PRD) and there has been rapid urbanisation around the PRD region in recent years. According to an air pollution report,[35] there has been an increase in the number of hazy days in Hong Kong. This observation might be attributed to the enhanced trapping of air pollutants by local urban land-sea breeze circulation, which is in turn related to increased emission of air pollutants over the PRD. The PRD region is closer to the New Territories and Kowloon Peninsula than Hong Kong Island, which might explain our findings of higher

Table 4 Associations of lead and cadmium with urinary albumin in 2063 subjects

Urinary albumin (mg/mmol UCr)	Blood Cd (nmol/L)	Urinary Cd (nmol/mmol UCr)	Blood Pb (nmol/L)	Urinary Pb (nmol/mmol UCr)
rho	−0.014	0.119	−0.121	0.151
p value*	0.521	<0.0001	<0.0001	<0.0001

* Compared by Spearman's coefficient of rank correlation (rho).

Table 5 Blood concentrations of Cd and Pb in general populations

Reference		Metals in blood* (nmol/L)		
Authors	Year	Cd	Pb	Notes
The present study	2011	6.41 (smoking, n=90) 3.02 (non-smoking, n = 1984)	118.0 (all)	Hong Kong school children (n = 2209)
Zhang *et* **al**.[36]	1999	5.43	221.3	Women in China (n = 250)
Zhang *et al*.[36]	1999	17.0	155.6	Women in Japan (n = 72)
Heitland *et al*.[37]	2006	3.38	91.79	Adult citizens in Germany (n = 130)
McKelvey *et al*.[38]	2007	10.85 (smoking, n = 449) 5.87 (non-smoking, n = 1036)	100.9 77.70	Adult citizens in New York (n = 1485)

* Expressed as geometric mean.

Table 6 Urine concentrations of Cd and Pb in general populations

Reference				Metals in urine* (nmol/mmol Cr)		
Author	Year	Age group, years	No. subjects	Cd	Pb	Notes
The present study	2011	1–5	700	0.29	0.67	Hong Kong school children
		6–10	193	0.30	0.72	
		11–15	1060	0.19	0.41	
		16–21	1003	0.21	0.42	
Heitland *et al*.[39]	2006	2–6	24	0.13	0.76	German children
		7–11	24	0.12	0.38	
		12–17	24	0.10	0.33	
Moon *et al*.[24]	2003	4–10	38	1.69†	3.77†	Korean children

* Expressed as geometric mean
† Measured by graphite-furnace atomic absorption spectrometry.

levels of Cd and Pb in blood and urine from children living in the New Territories and Kowloon than those from Hong Kong Island.

In summary, we reported the reference intervals of Cd and Pb in blood and urine in a Hong Kong general population. Blood Cd was affected by age, smoking and residential district while urinary Cd was influenced by age and blood Cd. Blood Pb was dependent on gender and residential district while urinary Pb was dependent on gender and blood Pb. Both urinary Cd and Pb were positively correlated with urinary albumin, and blood Pb affected haematopoietic indices in our subjects.

Acknowledgement: We thank subjects for their participation.

Conflicts of interest and sources of funding: The authors declare that there are no conflicts of interest to disclose.

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