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RESEARCH ARTICLE

Biological half-life of cadmium in the urine of inhabitants after cessation of cadmium exposure

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Abstract

We investigated the biological half-life of the urinary cadmium concentration (U-Cd) based on a 24-year follow-up study after cessation of cadmium exposure in a cadmium-polluted area. Spot urine samples were obtained from all inhabitants in this area in 1979, 1986, 1991, 1999 and 2003. Biological half-life was calculated in the inhabitants whose U-Cd was more than 5 $\mu g\,l^{-1}$ (9 men and 12 women) or 5 $\mu g\,g^{-1}$ creatinine (9 men and 19 women) using a one-compartment model. The estimated half-life and 95% confidence intervals were 13.6 years (9.0–28.2 years) and 13.9 years (9.6–25.6 years) for unadjusted U-Cd in men and women, respectively. For creatinine-adjusted U-Cd, they were 14.2 years (11.2–19.4 years) and 23.5 years (17.7–35.0 years) in men and women, respectively. The biological half-lives of U-Cd obtained in this study were identical with the values of total body burden determined by a different method.

Keywords: *Urinary cadmium; biological half-life; long-term follow-up study; risk assessment; human*

Introduction

Urinary cadmium concentration (U-Cd) and blood Cd concentration are generally adopted as an index of Cd body burden. Blood Cd concentration is considered to be related to recent exposure (Kjellström & Nordberg 1978, Lauwerys et al. 1979), and U-Cd to total body burden of Cd (Roels et al. 1981, Börjesson et al. 1997, Kido et al. 1992, 2004).

Mathematical models have been developed for calculations of Cd accumulation in renal and other tissues. Initially, one-compartment models of Cd metabolism in humans were used (Kjellström 1971, Tsuchiya & Sugita 1971). According to the one-compartment model, the whole-body half-life in humans was calculated to be at least 20 years. Subsequently a more elaborate eight-compartment physiologically based toxicokinetics model was developed (Kjellström & Nordberg 1978, Nordberg & Kjellström 1979). This model takes into account the transfer between the muscles, liver and kidneys, with the best fit of the empirical data obtained with 8–14 half-lives for each compartment. The multicompartment models have the possibility of calculating Cd concentrations in several tissues, including blood and U-Cd after Cd exposure. Choudhury et al. (2001) improved the multicompartment model that was developed by Nordberg and Kjellström (1979) and demonstrated good agreement between the Cd levels in urine generated by the model and the urine Cd levels measured in a population sample in the United States.

A few studies on the attenuation curves of the blood Cd of workers after cessation of exposure to Cd have been performed (Welinder et al. 1977, Järup et al. 1983, Kelman 1986). Welinder et al. (1977) followed 11 solderers for 15 months and reported that the biological half-life ranged from 25 to 146 days, the median values

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being 41 days, although a one-compartment exponential elimination model is too simple to describe the blood Cd curves. Järup et al. (1983) followed five previously exposed workers for a period of 10–13 years. The best fit to the observed data was obtained with a two-compartment model and the half-lives ranged from 75 to 128 days for the fast component and from 7.4 to 16.0 years for the slow component. Kelman (1986) followed nine workmen exposed to Cd. The blood Cd declined roughly exponentially, with a mean half-life of 20.4–31.3 months. On the other hand, attenuation and biological half-life of U-Cd have not been reported in man. In the present study, we investigated the biological half-life of U-Cd based on a 24-year follow-up study after cessation of Cd exposure in inhabitants of a Cd-polluted area.

Methods

Subjects

This study investigated all inhabitants of one hamlet in which the Cd concentration in rice was highest in the Kakehashi River basin in Ishikawa prefecture in 1974. Investigations were conducted in 1979, 1986, 1991, 1999 and 2003. The participants in each year were 98–105 men and 95–114 women, and participation rates were in the range of 82–85%. We selected inhabitants aged less than 50 years because younger inhabitants were unlikely to have renal tubular dysfunction at the beginning of the observation. Of these, the inhabitants who participated in all five urinary examinations and whose U-Cd was more than 5 $\mu g l^{-1}$ (9 men and 12 women) or 5 $\mu g g^{-1}$ creatinine (9 men and 19 women) were selected for calculation of the biological half-life (Table 1). Based on these criteria, the inhabitants whose U-Cd exceeded these values were considered to have been obviously exposed to Cd because in Ishikawa prefecture, the geometric mean of U-Cd grouped according to age did not exceed these values (5 $\mu g l^{-1}$ or 5 $\mu g g^{-1}$thinsp;cr) (Honda et al. 1981). The study protocol was approved by the Ethics Review Board of the Graduate School of Medicine, Chiba University.

Collection of samples and analytical method

We distributed polyethylene bottles treated beforehand with HNO_3 for urine sample to each family unit. Morning spot urine samples were collected and were kept frozen at –20°C on the same day. In 1979, U-Cd was determined by flameless atomic absorption spectrometry after wet ashing in $HNO_3/H_2SO_4/HClO_4$ and extraction with ammonium pyrolidine dithiocarbamate and methyl-isobutylketone (APDC/MIBK) (Honda et al. 1979). After 1986, U-Cd was determined directly by graphite-furnace atomic absorption spectrometry (Kido et al. 1984). Urinary creatinine was determined by the Jaffe reaction method (Bonness & Taussky 1945).

Statistical analysis

The one-compartment model was used to describe the decrease in urinary Cd levels over time. First, we

Table 1. Urinary cadmium of subjects grouped according to gender and age.

			1979		1986		1991		1999		2003	
Sex	Age (years) in 1979	N	GM	GSD	GM	GSD	GM	GSD	GM	GSD	GM	GSD
Urinary cadmium ($\mu g l^{-1}$)												
Males	18	1	13.4	NA	18.1	NA	0.5	NA	2.8	NA	2.5	NA
	25–32	4	8.3	1.5	7.2	2.4	4.0	1.4	4.0	2.7	2.9	1.2
	39–46	4	11.2	1.5	5.3	2.0	4.6	1.7	4.9	1.8	2.4	3.7
	Total	9	10.0	1.5	6.9	2.2	3.4	2.3	4.2	2.1	2.6	2.3
Females	18–22	2	10.7	1.0	8.4	1.1	4.4	1.2	3.1	1.3	5.1	1.3
	31	1	12.4	NA	14.5	NA	4.8	NA	14.1	NA	3.2	NA
	38–47	9	10.8	1.8	7.9	1.7	6.9	1.5	3.4	2.1	3.4	2.4
	Total	12	10.9	1.6	8.4	1.6	6.2	1.5	3.7	2.1	3.6	2.1
Urinary cadmium ($\mu g g^{-1}$ cr)												
Males	18	1	8.5	NA	6.8	NA	1.2	NA	1.8	NA	1.7	NA
	31–32	3	6.7	1.1	6.5	1.6	3.7	2.0	2.8	1.7	2.3	1.5
	35–46	5	8.2	1.2	6.2	1.2	4.0	1.8	3.6	1.2	2.8	1.6
	Total	9	7.7	1.2	6.4	1.3	3.4	1.9	3.1	1.4	2.4	1.5
Females	18–22	2	7.3	1.4	4.4	1.7	4.2	1.0	4.0	1.3	4.5	1.5
	25–31	3	9.8	1.4	5.6	2.0	5.1	1.6	5.5	1.6	4.2	1.4
	38–47	14	11.6	1.6	9.2	1.4	9.7	1.3	5.5	1.5	5.9	1.5
	Total	19	10.8	1.5	7.9	1.6	8.0	1.5	5.4	1.5	5.4	1.5

GM, geometric mean; GSD, geometric standard deviation; NA, not available.

estimated parameters for the relationship between log-naturally transformed unadjusted U-Cd or creatinine-adjusted U-Cd and time (years) by using the following one-compartment model (1) in each subject.

$$\mathrm{Ln(u-cd)} = \alpha \times \mathrm{time\,(year)} + \beta \quad (1)$$

Ln indicates the natural logarithmic function, β indicates the intercept for U-Cd. Then, according to the distribution of slopes (α in Equation 1) of subjects grouped according to gender, mean and 95% confidence intervals of the slope were calculated and then transformed to biological half-life using the following equation (2).

$$\text{Biological half-life} = \frac{\mathrm{Ln}(2)}{\alpha} \quad (2)$$

The analyses were performed with SPSS 12.0.1J software (SPSS Japan Inc., Tokyo).

Results

Table 1 shows the geometric mean and geometric standard deviation of unadjusted ($\mu g\,l^{-1}$) and creatinine-adjusted ($\mu g\,g^{-1}$ cr) U-Cd grouped according to gender and age. There was a trend for both unadjusted and adjusted U-Cd to decrease with later measurement after cessation of Cd exposure.

Table 2 shows the estimated biological half-life of unadjusted and adjusted U-Cd grouped according to gender. The estimated half-life and 95% confidence interval were 13.6 years (9.0–28.2 years) and 13.9 years (9.6–25.6 years) for unadjusted U-Cd in men and women, respectively. The obtained half-life was similar between men and women. For creatinine-adjusted U-Cd, they were 14.2 years (11.2–19.4 years) and 23.5 years (17.7–35.0 years) in men and women, respectively. When men and women were combined, the estimated half-life was 13.8 years and 19.4 years for unadjusted and adjusted U-Cd, respectively.

Table 2. Estimated biological half-life of urinary cadmium grouped according to gender.

	Estimated biological half-life (years)
	Mean (95% CI)
Urinary cadmium ($\mu g\,l^{-1}$)	
Males	13.6 (9.0, 28.2)
Females	13.9 (9.6, 25.6)
Total	13.8 (10.5, 20.0)
Urinary cadmium ($\mu g\,g^{-1}$ cr)	
Males	14.2 (11.2, 19.4)
Females	23.5 (17.7, 35.0)
Total	19.4 (15.8, 25.1)

95% CI, 95% confidence interval.

Discussion

In the Kakehashi River basin in Ishikawa Prefecture, several areas were highly polluted by Cd originating from an upstream mine, and adverse health effects were observed in inhabitants of these areas (Department of Health, Ishikawa Prefecture 1976). The rice Cd concentration in the target area was 0.67 ppm, which indicates the most marked degree of pollution in areas in the Kakehashi River basin (Department of Health, Ishikawa Prefecture 1976). The target area was surrounded by rice fields and was a common type of farm village in the Kakehashi river basin. There were no factories around the target area. Most inhabitants own private rice fields. Inhabitants without their own rice fields also ate rice grown in the target area. In 1970, daily Cd intake was investigated in three men and three women using the total diet method (Department of Health, Ishikawa Prefecture 1976). Daily Cd intake was 178 μg daily and 211 μg daily and 20% and 15% of the daily intake were from rice in men and women, respectively. Investigation of eight foodstuffs other than rice revealed significant differences in the Cd concentration in potato (0.097 ppm vs 0.042 ppm) and cucumber (0.008 ppm vs 0.0021 ppm) between Cd polluted and non-polluted areas. Therefore, it can be concluded that the Cd intake of inhabitants in Cd-polluted areas originated in the rice polluted with Cd. After 1977, polluted soil in rice fields was removed, and unpolluted soil added. This work was completed in 1979. In 1980, rice and soil samples were collected from 13 points in the rice fields of 66 hectares after the soil replacement. The mean Cd concentrations were 0.05 ppm in rice and 0.04 ppm in the soil (Department of Environment, Ishikawa Prefecture 1980), corresponding to the values in non-polluted areas. Therefore, it is certain that the environmental Cd exposure in the target area ceased after soil replacement.

The measurement method of U-Cd differed in 1979 and the other years. However, the correlation coefficient and estimated regression equation of values in 25 samples determined by these two methods were 0.973 and $Y = 0.98X - 0.30$. Thus, the values of measurement by these methods were in accord with each other, indicating the absence of systematic methodological error (Kido et al. 1984). As noted above, Järup et al. (1983) used one-compartment and two-compartment exponential elimination models to describe the decrease in blood Cd levels over time. The best fit to the observed data was obtained with a two-compartment model. The estimated slow component of the biological half-life (7.4–16.0 years) is in accordance with the model proposed by Kjellström and Nordberg (1978) and earlier estimation of the total body and kidney biological half-life (Friberg et al. 1974). Most blood Cd is accumulated in the cell. Therefore, the fast component may merely

reflect the turnover of cells in the blood. To evaluate whether the two-compartment model fit better to the attenuation curve of Cd after elimination of exposure, we calculated the biological half-life in a dataset consisting of the initial three consecutive measurements (1976–1991). The biological half-life of these three consecutive measurements was 7.9 years in men and 15.0 years in women for unadjusted U-Cd and 10.7 years in men and 26.7 years in women for adjusted U-Cd. Thus, we did not obtain an apparently shorter biological half-life than those obtained based on all five consecutive measurements. Therefore, the two-compartment model did not show an obviously better fit to the data than did the one-compartment one. Furthermore, it was reported that the U-Cd stayed at almost the same level, whereas the blood Cd level increased rapidly after Cd exposure started in Cd workers (Kjellström & Nordberg 1978, Lauwerys et al. 1979). Therefore, it is appropriate to consider that the fast component does not exist for U-Cd attenuation.

The estimated mean half-life of 13.6–23.5 years is somewhat longer than the half-life of blood Cd in the slow component reported by Järup et al (1983). However, the biological half-life of total Cd body burden was suggested to be 10–30 years in man (Nordberg et al. 1985). Yamagata et al. (1975) studied the retention of Cd in the body of subjects who had ingested rice containing ^{115}Cd. Using a two exponential elimination model, they calculated the biological half-life of the slow component to be 20 years or more. Shaikh and Smith (1980) studied 12 volunteers who ingested beef kidney containing ^{115}Cd or ^{109}Cd to observe the whole-body retention. The best fit to the data was three exponentials and the biological half-lives were 1.58, 33.7 and 9605 days (26.3 years), respectively. These are the only studies which have calculated the biological half-life of body burden of Cd based on the real observation of retention of Cd.

During the early phase of exposure, the U-Cd is mainly related to the body burden (Nordberg 1972). When cadmium-induced renal damage has occurred, urinary excretion increases (Nordberg & Piscator 1972). Cadmium-exposed people with proteinuria generally have higher cadmium excretion than such people without proteinuria (Lauwerys et al. 1974, Kojima et al. 1977). In the present study, U-Cd sufficiently represented the total body burden because we selected younger inhabitants who were unlikely to have renal dysfunction.

In conclusion, the present study first calculated the biological half-life of urinary Cd in the inhabitants of a Cd-polluted area of Japan which was based on a long observation of urinary Cd concentrations after cessation of exposure and demonstrated that the biological half-life of urinary Cd obtained in the present study is similar to the half-life of total Cd body burden previously reported.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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