Renal cadmium overload without nephrotoxicity

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ABSTRACT A redundant nickel/cadmium battery worker was investigated for non-specific fatigue after completing five years in the industry. Sensitive techniques for in-vivo organ cadmium measurement showed a moderate accumulation in the liver but a very large concentration in the kidneys. Despite this, overall glomerular and tubular function were not impaired. It was concluded that the mechanism of proteinuria observed in some cadmium workers is obscure and not clearly related to the degree of kidney saturation with cadmium.

Workers in the cadmium industry develop tubular proteinuria and occasionally a reduction in overall renal function.¹ The underlying mechanism of the renal disturbance is uncertain, but a critical renal cortical cadmium concentration has been proposed, which when exceeded may result in renal dysfunction.² A recent survey of occupationally exposed workers confirmed earlier estimates that the critical renal cortical cadmium concentration was 200-250 $\mu\text{g/g}$ wet weight.³ This corresponded to a hepatic concentration of 39-48 $\mu\text{g/g}$ and a urinary cadmium concentration of 10-15 $\mu\text{g/g}$ creatinine. We have studied a worker exposed to cadmium who was found to have an excessive level of renal cortical cadmium concentration, 400 $\mu\text{g/g}$ wet weight, without evidence of renal dysfunction or proteinuria, and express reservations about this concept.

Case report

A 37-year-old male worker who had been employed in a nickel/cadmium battery factory for five years was investigated four months after redundancy. He smoked 30 cigarettes a day. During his employment he never used protective gloves and dipped his hands into cadmium-containing fluid daily. Results from routine clinical and biochemical tests were normal; blood pressure was 130/80 mm Hg. An intravenous urogram showed two normal sized kidneys with normal pelvicalyceal systems and no sign of calculus.

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Received 31 July 1980

Accepted 10 September 1980

Methods

Neutron activation measurement of kidney and liver cadmium was applied to this patient, using a sensitive apparatus that had been developed for analysis in non-occupationally exposed people.⁴ This instrument has a lower limit of detection (2 SD of the background) of 3.2 mg of cadmium in the kidney and 2.7 $\mu\text{g/g}$ in the liver for a localised skin dose of 800 mrem delivered in 33 minutes. Glomerular filtration rate and effective renal plasma flow were measured by plasma clearance of ⁵¹Cr EDTA and ¹²⁵I Hipuran respectively.⁵

Results

The patient had a kidney content of 39 ± 4 mg and a liver concentration of 8 ± 3 $\mu\text{g/g}$ cadmium compared with a mean value of 3.8 mg in the kidneys of 60 non-exposed subjects (both smokers and non-smokers) measured under the same conditions.⁶ Using the formulation of Roels *et al*,³ a kidney content of 39 mg cadmium converts to a renal cortex concentration of 400 $\mu\text{g/g}$ (wet weight) assuming a 145-g kidney and a ratio of 1.5 between cortex and whole organ concentrations. Blood (28.3 $\mu\text{g/l}$) and urine (14.4 $\mu\text{g/g}$ creatinine) cadmium concentrations were both raised, but renal function was effectively normal with a glomerular filtration rate of 106 ml/min/1.7 m² (normal 115) and an effective renal plasma flow of 524 ml/min/1.7 m² (normal 603). Serum creatinine concentration was normal at 1.1 mg/100 ml. A 24-hour specimen of urine contained trace amounts of protein only, while radioimmunoassay of β_2 -

microglobulin (Phadebas β_2 Microtest) yielded normal values of 19 $\mu\text{g/g}$ creatinine in urine and 1.39 mmol/l in serum. Urinary lysozyme activity was nil. Maximal urine osmolality was 600 mOsm/kg.

Comment

A renal cortical concentration of cadmium of 400 $\mu\text{g/g}$ was observed in our patient with no indication of either glomerular or tubular proteinuria, even though the blood and urine cadmium concentrations were at levels where such dysfunction is considered to be increasingly probable.^{3,7} It is also noteworthy that the ratio of renal cortical to liver concentration was almost 50, compared with a mean ratio of 5 reported by Roels *et al.*,³ and an expected ratio of about 20 if both liver and kidney contain similar total amounts of the metal.

Initial estimates of a critical renal cortical cadmium concentration were based on necropsy and biopsy data which displayed a wide range of values up to 446 $\mu\text{g/g}$.² Nevertheless, an in-vivo study of 309 workers supported the view that the critical concentration lay between 200 and 250 $\mu\text{g/g}$,³ although Nomiya *et al.*⁸ reported a higher concentration of 380–470 $\mu\text{g/g}$ in experiments with monkeys. A further in-vivo survey at a cadmium plant in the United States yielded values of renal cortical cadmium concentration ranging up to 590 $\mu\text{g/g}$ in workers with no evidence of renal impairment, with a best estimate of a critical value being somewhat above 300 $\mu\text{g/g}$.⁹ It is apparent, therefore, that kidney dysfunction is not clearly related to the concentration of cadmium in the kidney, and that the concept of criticality must apply to some other aspect of cadmium metabolism.

Cadmium in the liver and kidney is found mainly as the metallothionein, Cd-thionein, whose synthesis can occur independently in each organ.¹⁰ Induction of metallothionein in mammals is considered to be a protective mechanism against the toxic cadmium ion, although isolated Cd-metallothionein is toxic to renal tubular lining cells when given by intravenous injection. It has been suggested, therefore, that kidney dysfunction is related to an increase in plasma Cd-metallothionein,¹¹ which may in turn be dependent on the hepatic content of the complex.¹⁰

Such a hypothesis might explain the findings reported here if it is assumed that the rate and type of exposure induced renal metallothionein in preference to hepatic metallothionein, and that renal dysfunction has been avoided by the relatively low accumulation in the liver and a correspondingly negligible transport of metallothionein from the liver to the kidney.

This suggests that the concept of a critical renal cortical cadmium concentration should be modified

to take account of the conditions of exposure and of the relative amounts of cadmium in the kidneys and the liver. Longitudinal studies of workers exposed under various conditions would be helpful in relating uptake and distribution of cadmium with circulating concentrations of Cd-metallothionein and indices of renal function.

We thank Dr A C Ames and Mr A Thomas for providing the blood and urine cadmium results, and the x-ray department at Singleton Hospital for performing the ultrasound scans. The neutron activation instrument was developed with the help of Professor J Dutton and Dr C J Evans of Swansea University College and Mr A Sivyver and staff of the medical physics department at Singleton Hospital. Financial support was provided by a Science Research Council CASE studentship for one of us (PEC) and a grant from the Welsh Scheme for the Development of Health and Social Research. We are also grateful to Miss Julie E Davies for secretarial help.

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