CADMIUM CONCENTRATION IN BLOOD AND ALTERATIONS IN THE RATE OF ANTIPYRINE METABOLISM IN MAN

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ABSTRACT

The study was undertaken in a group of 129 subjects: 68 healthy persons and 61 atherosclerotic patients with or without heart and renal failure. In healthy subjects blood cadmium concentration was 0.74 ± 0.29 μg/100 cm³. A positive correlation was found \((r = 0.61)\) between cadmium concentration in the blood and biological half-time of antipyrine elimination. This suggests that environmental contamination by cadmium may contribute to inhibition of the activity of hepatic metabolizing enzymes in healthy subjects. In the group of patients with renal or heart failure cadmium concentration in the blood was low \((0.56 ± 0.28 \mu g/100 \text{ cm}^3)\) probably due to proteinuria. No correlation was found between cadmium concentration in the blood and antipyrine elimination.

Cadmium has long been known as an industrial environmental toxicant. It is an important metal with widespread application in industry, notably in metallurgy, nuclear and electrical engineering, and in the paint and pigment industry. Cadmium represents a health hazard to man of proportion which has not yet been defined. Absorbed cadmium is excreted very slowly and the body burden increases with age. Prolonged cadmium exposure is known to produce liver and kidney damage in both animals and humans. Recent studies have reported that the duration of drug response is altered after the administration of cadmium salts. After cadmium exposure various pathological changes have been reported to occur in the liver, such as focal necrosis, fibrosis, fatty infiltration, cirrhosis and inflammation. Within the hepatocyte both the microsomal and mitochondrial fractions rapidly accumulate cadmium. The present study was undertaken to investigate whether cadmium pollution could modify responsiveness to drugs in man or not. Antipyrine elimination from the body was used as an index of liver capacity to metabolize drugs.

SUBJECTS AND METHODS

A total of 129 subjects were divided into three groups:
1. Healthy subjects, 68 habitants of Łódź (29 women and 39 men, the average age 39.6 ± 11.3 y).
2. 34 patients with atherosclerotic disease without heart or renal failure (17 women + 17 men, the average age 44.8 ± 13.9 y).
3. 27 atherosclerotic patients with congestive heart failure and chronic renal failure (13 patients). The group consisted of 13 women and 14 men, the average age 66.0 ± 9.2 y.

Plasma-creatinine concentration in patients with renal failure exceeded 1.5 mg/100 ml.

Data on smoking habit were available for all subjects. No subject was occupationally exposed to cadmium.

Antipyrine kinetics

All subjects received an oral dose of 1.2 g of antipyrine after an overnight fast. Six peripheral venous blood samples were taken in 3, 6, 9, 12, 24 and 48 hours after antipyrine administration. Antipyrine was analysed by the spectrophotometric method of Brodie and associates. Assuming one-compartment model, the clearance of antipyrine (Cl) was calculated as shown in equation: Cl = Vd \frac{0.693}{T_{1/2\beta}}$, where volume of distribution Vd = \frac{Dose}{\beta}$, and $\beta$ was estimated from the least squares regression analysis.

Blood-cadmium determination

Two milliliters of venous blood was collected with heparin in containers prewashed in 10% HNO$_3$ and rinsed carefully. The amount of 0.5 ml blood was treated with 0.3 ml 70% perchloric-acid and 0.6 ml perhydrol. After three hours of heating at 60°C the sample was ready for determination. Atomic absorption spectrophotometer Beckman 1248 with hellow cathode lamp as well as deuterium lamp and Massman Cuvette 1268 were used. Programme temperature: drying phase 100°C - 20 s, ashing phase 400°C - 30 s, atomization phase 2000°C - 10 s, burning-out phase 2900°C - 3 s. As a rule, three isolated samples were prepared and determined from each blood sample. Accuracy of the method ± 6%, detection limit 0.1µg%.

RESULTS

The results of investigation in the group of healthy subjects are presented in Table 1. No difference was observed in blood cadmium concentration between women and men. A positive correlation (r = + 0.61, p < 0.05) was found between blood cadmium (x) and biological half-time of antipyrine (y), according to equation: y = 5.49x + 8.95 (Figure 1). The correlation was observed in the group of cigarette smokers (r = + 0.50), as well as in non-smokers (r = + 0.77).

In the group of atherosclerotic patients without renal or heart failure (Table 2) the blood cadmium concentration was higher (0.91 ± 0.43 µg/100 cm$^3$) than in the group of healthy subjects (0.74 ± 0.29 µg/100 cm$^3$, p < 0.05) and the
TABLE 1
Blood cadmium concentrations and kinetics of antipyrine in 68 healthy subjects.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Blood cadmium µg/100 cm³</th>
<th>Antipyrine kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>k₂</td>
</tr>
<tr>
<td>Smokers</td>
<td>38</td>
<td>X 0.84 S.D. 0.26</td>
<td>0.055</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>30</td>
<td>X 0.62 S.D. 0.28</td>
<td>0.057</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>X 0.74 S.D. 0.29</td>
<td>0.056</td>
</tr>
</tbody>
</table>

FIG. 1 - Correlation between blood cadmium concentration and biological half-time of antipyrine elimination in healthy subjects.

elimination of antipyrine was decreased. No correlation was found between blood cadmium and half-time of antipyrine in this group of patients.

In the group of atherosclerotic patients with renal and/or heart failure (Table 3) the average blood cadmium level was smaller (0.56 ± 0.28 µg/100 cm³) than in the group of healthy subjects (p < 0.05) and patients without renal or heart failure (p < 0.01). Simultaneous elimination of antipyrine was very slow. No correlation between cadmium level in the blood and biological half-time of antipyrine was found.
TABLE 2
Blood cadmium concentrations and kinetics of antipyrine in 34 atherosclerotic patients without heart or renal failure.

<table>
<thead>
<tr>
<th></th>
<th>Blood cadmium</th>
<th>Antipyrine elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg/100 cm³</td>
<td>k₂ (h⁻¹)</td>
</tr>
<tr>
<td>Smokers</td>
<td>15 X</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>S.D. 0.42</td>
<td>0.017</td>
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<tr>
<td>Non-smokers</td>
<td>19 X</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>S.D. 0.42</td>
<td>0.020</td>
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<tr>
<td>Total</td>
<td>34 X</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Among healthy and diseased subjects alike smokers showed significantly higher blood-cadmium levels than non-smokers.

TABLE 3
Blood cadmium concentrations and kinetics of antipyrine in 27 atherosclerotic patients with chronic renal and/or heart failure.

<table>
<thead>
<tr>
<th></th>
<th>Blood cadmium</th>
<th>Antipyrine kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg/100 cm³</td>
<td>k₂ (h⁻¹)</td>
</tr>
<tr>
<td>Smokers</td>
<td>7 X</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>S.D. 0.18</td>
<td>0.009</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>20 X</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>S.D. 0.26</td>
<td>0.013</td>
</tr>
<tr>
<td>Total</td>
<td>27 X</td>
<td>0.56</td>
</tr>
</tbody>
</table>

DISCUSSION

The concentration of cadmium in blood may be considered as an index of actual cadmium exposure. Cadmium air contamination in Polish towns varies from 0.002 to 0.051 µg/m³, in Łódź an average level is 0.005 µg Cd/m³. In healthy subjects we found blood cadmium from a trace amount (< 0.1 µg/100 cm³) to 1.5 µg/100 cm³, the mean level was 0.74 (S.D. 0.29) µg/100 cm³. Our results correspond to the results of other authors who reported the mean values
of blood cadmium in healthy subjects from 0.13 to 0.95 µg/100 cm³, and only exceptionally higher. The differences in blood cadmium between smokers and non-smokers found here and elsewhere confirm that cigarette smoke is an important source of cadmium for the body. In healthy subjects who were not occupationally exposed to cadmium we found a marked positive correlation between cadmium concentration in the whole blood and biological half-time of antipyrene. This indicates that an increase of blood cadmium level is accompanied by a decrease of liver capacity to metabolize antipyrene.

Many enzymatic reactions are involved in the metabolism of xenobiotics. The most widely studied one is the microsomal cytochrome P-450 oxidase system. Trace elements may alter the synthesis or degradation of various haems of flavoprotein components, affecting electron transfer reactions. Information on the alteration of drug metabolism by trace elements is rapidly increasing. Several cations stimulate (Ca²⁺, Mg²⁺, Mn²⁺, Sr²⁺), while others inhibit (Ca²⁺, Fe³⁺, Zn²⁺) drug metabolism and cytochrome P-450 activity. Evidence was presented that the administration of cadmium impaired hepatic drug metabolizing enzymes in animals. Hadley and co-workers showed that rats and mice pretreated intraperitoneally with cadmium acetate, prior to carrying out drug metabolic assays, exhibited marked inhibition in drug metabolism three days after the injection of a relatively high dose of 2.0 mg/kg of body weight. Similar results were shown by other authors. Unger and Clausen reported that the inhibition of hepatic drug metabolizing enzyme by cadmium was well related to the accumulated content of cadmium in mouse liver when measured four days after the treatment with cadmium nitrate. Reversely, Wagstaff utilizing unrealistically high dietary levels of cadmium found no inhibition of hepatic drug metabolism. In fact he reported stimulation of drug metabolism 15 days after commencing his dietary regimen. Yohida and co-workers demonstrated that metallothionein may be involved in the biological protection of animals against the inhibition of drug metabolizing enzymes by cadmium.

Our results suggest that environmental contamination by cadmium may contribute to inhibition of hepatic drug metabolizing enzymes in healthy subjects. On the contrary, in the group of atherosclerotic patients with or without renal and heart failure, no correlation was found between blood cadmium levels and the rate of antipyrene elimination. In patients, both antipyrene elimination and blood cadmium level were involved in several pathological processes. The biological half-time of antipyrene was significantly longer in atherosclerotic patients than in healthy subjects, as a consequence of circulatory disorders and secondary hepatic injury. Blood cadmium in atherosclerotic patients without heart or renal decompensation was higher than in normal subjects, but when heart and/or heart failure occurred, blood cadmium became significantly lower than in the group of healthy persons. It was probably a consequence of proteinuria and a loss of cadmiothionein in urine. It is known that in workers occupationally exposed to cadmium, cadmium in urine increased, when renal injury occurred.
REFERENCES


