Absorption Rates of Cadmium Orally Administered in a Single Dose to Rats, and the Sites in the Digestive Canal Primarily Concerned in Absorbing Cd

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INTRODUCTION

There is much evidence in the reports that cadmium is toxic to man and animals\(^1\). Beton et al.\(^2\) (1966) reported a fatal case associated with bilateral cortical necrosis of the kidneys. Wisniewska-Knypl et al.\(^3\) (1971) reported a case of acute cadmium poisoning. Friberg\(^4\) (1950) showed that prolonged exposure to cadmium gave rise to renal damage.

In Japan, Murata et al.\(^5\) (1969) found that cadmium produced shortening and thickening of the villi of the duodenum in Japanese women eating cadmium contaminated food. However, it is not clear whether chronic oral cadmium poisoning exists in men.

If chronic cadmium poisoning caused by the oral intake of cadmium has occurred in men, it is important to prove a causal relationship between the balance of cadmium, the storage in the body, and tissue damage. These points must be proven by experimentation as the first step, but there is little data available at present.

A few studies have investigated the absorption rates of ingested cadmium; the 1.9% uptake in livers and kidneys 24 hrs after \(^{115m}\)Cd(NO\(_3\))\(_2\) was orally administered in a single dose to rats\(^6\), the 0.5–8% uptake in carcasses 24 hrs after \(^{109}\)CdCl\(_2\) was orally administered in a single dose to mice\(^7\), the 2% uptake in carcasses 24 hrs after CdS was orally administered in a single dose to mice\(^8\), and the 2.8–11.4% uptake in carcasses 24 hrs after \(^{115m}\)CdCl\(_2\) was administered in a single dose to mice fed 10 days with various diets\(^9\). Although cadmium is poorly absorbed it accumulates in the kidneys and the liver throughout life and is not extensively excreted.

This study was undertaken to determine the apparent absorption of \(^{109}\)Cd in intact rats and to determine the absorption from various sections of the rat’s gastrointestinal tract.

METHOD

Absorption rate of cadmium from the digestive canal. Six male rats of the Donryu strain (average weight, 207 g) that had been fed a commercial laboratory diet and tap water ad libitum, were starved for 12 hrs before the experiment. A single dose of 5.0 µCi of \(^{109}\)CdCl\(_2\) (carrier free) was administered directly to the stomach by a stomach tube while the animals were under light anesthesia with ether. The total amount of administered cadmium was approximately 1.0 nano g. The radioactivity of the whole body of the living animals which was kept constant was determined with a gamma-ray scintillation counter immediately after administration of the radio-cadmium.

Twenty-four hours after administration of the \(^{109}\)CdCl\(_2\), the animals were killed with ether and immediately resected from the lower part of the esophagus to the anus. Radioactivity of the carcass (whole body except for the resected portions) and the resected digestive

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canal were determined with the same counter. The rate of uptake in the carcasses was called the absorption rate in this case.

Differences in absorption of cadmium by site in the digestive canal. Ten male rats of the Donryu strain (average weight, 300 g) that had been fed a commercial laboratory diet and tap water ad libitum, were starved for 12 hrs before being killed by decapitation. The stomach, small intestine, colon, and caecum were immediately resected.

Sac techniques. The simple everted sac method\(^1\) was used. Sacs were prepared from different regions of the small intestine, stomach, colon, and caecum. The small intestine was trisected, and the upper proximal 10 cm, except for the intestinal openings of the biliary and pancreatic ducts, was used. The middle part used was the central 10 cm, and the lower part the distal 10 cm. The proximal 10 cm of the colon also was used.

The intestine was carefully cleaned of mesenterium rests and adipose tissue. Each strip was everted and washed in ice-cold 0.3% glucose-0.9% NaCl solution, then weighed. One end of the strip was ligated; the second end (free end) was ligated soon after injecting 1 ml of the medium (pH 7.0, except for the stomach which was pH 3.5) in it. Twenty milliliters of medium containing \(^{109}\)CdCl\(_2\) at the rate of 0.1 \(\mu\)Ci/ml, and each everted strip were put in 100 ml Erlenmeyer flasks and shaken at a rate of 70 rounds per minute at 37\(^\circ\)C. The total amount of administered cadmium was approximately 0.4 nano g. The intrafluid of the strip was the serosal fluid and the extrafluid was the mucosal fluid.

Ninety minutes after shaking, each strip was washed in ice-cold 0.9% NaCl solution. The radioactivities of the filtered serosal fluid, and that adhering to or absorbed into the cell wall were measured with a well-type scintillation counter. In measuring the radioactivity the counting error was less than 0.5%.

The purity of the carrier-free \(^{109}\)CdCl\(_2\) (New England Nuclear Corp) used in both experiments, was determined by the spectrum of its gamma-ray and was ascertained to have no gamma-ray of other nuclides. Composition of the medium. Glucose, 200 mg/dl, NaCl, 145 mM, KCl, 5 mM, MgCl\(_2\), 2 mM, and Tris (2-amino 2-hydroxymethyl propane 1:3 diol), 10 mM.

**RESULTS**

Radioactivity in the whole body of rats immediately after the oral administration of cadmium and in the carcasses 24 hr after administration is shown in Table 1. The average

<table>
<thead>
<tr>
<th>Rat NO.</th>
<th>Body Weight</th>
<th>Whole Body*</th>
<th>Carcass**</th>
<th>Absorption Rate***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>215 gm</td>
<td>6,109 cpm</td>
<td>105 cpm</td>
<td>1.72%</td>
</tr>
<tr>
<td>2</td>
<td>210</td>
<td>7,388</td>
<td>128</td>
<td>1.73</td>
</tr>
<tr>
<td>3</td>
<td>195</td>
<td>7,513</td>
<td>250</td>
<td>3.33</td>
</tr>
<tr>
<td>4</td>
<td>251</td>
<td>7,439</td>
<td>74</td>
<td>0.99</td>
</tr>
<tr>
<td>5</td>
<td>178</td>
<td>16,953</td>
<td>461</td>
<td>2.72</td>
</tr>
<tr>
<td>6</td>
<td>194</td>
<td>15,977</td>
<td>163</td>
<td>1.02</td>
</tr>
<tr>
<td>mean</td>
<td>207</td>
<td>10,230</td>
<td>197</td>
<td>1.92</td>
</tr>
</tbody>
</table>

* Radioactivity of the whole body of live animals immediately after administration of 109-CdCl\(_2\)
** Radioactivity of the carcass (whole body except for the lower part of the esophagus to the anus) 24 hr after administration of 109-CdCl\(_2\)
*** Radioactivity of carcass/Radioactivity of whole body \(\times 100(\%)\)
rate of absorption of cadmium in six rats was 1.92% (range 0.99 to 3.33%). The radioactivity in the whole body of rats Nos. 5 and 6 was more than twice that in the others since the administered dose was double.

The transported $^{109}\text{Cd}$ from the mucosal to serosal fluid per gram at each site in the digestive canal is shown in Figure 1. The radioactivity in the serosal fluid of the small intestine was significantly higher ($p<0.01$) than at other sites in the digestive canal. The value for the stomach was significantly lower ($p<0.05$) than that for the caecum or colon. The transportation of cadmium per gram at each site in the digestive canal from the mucosal to the serosal fluid was easily transported in the following order; each part of the small intestine, the caecum and colon, and the stomach. If converted to the transported amount of cadmium per whole organ based on the weight of each strip, this trend is remarkable.

The ratio of the transported amount by each digestive organ compared to the entire digestive tract was stomach 1.4%, small intestine 86.7%, caecum 6.3%, and colon 5.7%. In the small intestine, the upper, middle, and lower parts were 27.6, 32.2 and 26.9%, respectively. The absorption of inorganic cadmium compounds of trace dose, suggests that the small intestine plays the largest role in absorbing cadmium.

The radioactivity in the cell wall per gram of each strip is shown in Figure 2. The stomach had significantly higher radioactivity ($p<0.01$) than others. The caecum was significantly lower ($p<0.05$) than each site in the intestine and colon. There was no statistical difference in the three parts of the small intestine, in the colon, and in each site of the intestine. Characteristically in the stomach, the transported amount of $^{109}\text{Cd}$ from the mucosal to serosal fluid was extremely small, although the amount of $^{109}\text{Cd}$ in the cell wall was very large.
DISCUSSION

When $^{109}\text{CdCl}_2$ was administered orally in a single dose to rats, only 1.92% passed into the body within 24 hrs. This compares with the 0.5 to 8% for mice\textsuperscript{7} and about 2% for goats\textsuperscript{11} and 18% for cows\textsuperscript{12}. In man it is estimated that between 1 and 4% of the daily intake of 30–60 µg of cadmium is absorbed\textsuperscript{13}. Decker et al.\textsuperscript{6} (1957) reported that the uptake in the liver and kidney 24 hrs after $^{115}\text{mCd(NO}_3)_2$ was administered orally in a single dose to rats was 1.9%. Because cadmium added the diet of experimental animals accumulates in the liver and kidneys\textsuperscript{14}, our results are similar to those demonstrated by Decker. The absorption rates of some other metals administered orally to rats are shown in Table 2. Although numerous factors influence cadmium absorption from the intestine\textsuperscript{15–17}, our results indicate that cadmium may belong in the lower absorption rate group of these metals.

The transported amount of cadmium from the mucosal to the serosal fluid using the simple everted sac method was highest in the small intestine and lowest in the stomach, not only per gram at each site in the digestive canal but per whole organ. Cadmium absorption is characteristically uniform throughout the small intestine. Sahagian et al.\textsuperscript{18} (1966) reported that the jejunum was the least absorptive section of the rat intestine for cadmium, but the effects of residence time and digesta passage rates were not considered in their in vitro studies, even though the fastest rates of passage occur in the duodenum; but the digesta residence time is almost 20 times longer in the distal small intestine than in the duodenum\textsuperscript{19,20}. Suffice it to say the small intestine is the active site of absorption of cadmium, based on the everted sac method.

The active absorption sites of other metals are shown in Table 3. Interestingly cadmium shows no absorption difference in the segments of the small intestine as does molybdenum.

However, the absorption of $^{109}\text{Cd}$ probably depends upon the area of the absorptive surface, and since the thickness of the wall at each site in the digestive canal and the structure of the mucosal epithelium varies, the transported amounts of $^{109}\text{Cd}$ per gram of tissue may not reflect the true pattern of cadmium absorption.

It is difficult to accurately measure the mucosal surface area, but when the mucosal epithelium at each site in the digestive canal of the control animals (weight, 274 and 307 g) were stripped off and the net weight determined, the percentage of mucosal epithelium per gram at each of the six sites in the digestive canal was nearly the same. If the quantity of mucosal epithelium is proportioned to the mucosal surface area, then the reason for the differences in the active site of cadmium absorption in the digestive canal are the same as for the mucosal surface area.

Because there are different patterns for the transported amounts of cadmium and the

<table>
<thead>
<tr>
<th>Metals</th>
<th>Absorption rate %</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>6</td>
<td>23)</td>
</tr>
<tr>
<td>Nickel</td>
<td>1</td>
<td>24)</td>
</tr>
<tr>
<td>Aluminium</td>
<td>1.5</td>
<td>25)</td>
</tr>
<tr>
<td>Copper</td>
<td>2.3</td>
<td>26)</td>
</tr>
<tr>
<td>Strontium</td>
<td>55</td>
<td>27)</td>
</tr>
<tr>
<td>Manganese</td>
<td>3–4</td>
<td>28)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>17</td>
<td>29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metals</th>
<th>Sites of absorption</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Proximal s. intestine</td>
<td>30)</td>
</tr>
<tr>
<td>Iron</td>
<td>Upper jejunum</td>
<td>31)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Proximal s. intestine</td>
<td>32)</td>
</tr>
<tr>
<td>Strontium</td>
<td>Distal s. intestine</td>
<td>33)</td>
</tr>
<tr>
<td>Copper</td>
<td>Stomach</td>
<td>34)</td>
</tr>
<tr>
<td>Zinc</td>
<td>Duodenum</td>
<td>34)</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>Stomach &amp; s. intestine</td>
<td>34)</td>
</tr>
</tbody>
</table>
detected amounts of cadmium in the cell walls of the tissues, cadmium transport is not due to simple permeability of the membrane; it may be due to different functions of the mucosal epithelium at each site in the digestive canal.

The sequestration of cadmium by the intestinal mucosa may protect the body against toxic effects\(^2\). The sequestration of cadmium by the stomach may have the same function, because we observed that cadmium uptake was at a maximum in the stomach.

The main active site of cadmium absorption was confirmed to be the small intestine. Therefore, we may be able to study the absorption mechanism of cadmium and characteristics of this absorption under the different conditions in a living body.

**SUMMARY**

The absorption rate of cadmium orally administered in a single dose to rats, and the sites in the digestive canal primarily concerned in absorbing cadmium were studied. The following results were obtained:

1. When \(^{109}\text{CdCl}_2\) was orally administered in a single dose to rats, the average absorption rate of cadmium 24 hrs after administration was 1.92% (range, 0.99 to 3.33%).
2. The transported amounts of cadmium from the mucosal to the serosal fluid in the simple everted sac method were highest in the small intestine and lowest in the stomach.
3. Cadmium absorption was characteristically uniform throughout the small intestine.

**REFERENCES**


