INTRODUCTION

The crucial moment of Ca-DTPA (calcium salt-diethylenetriaminepentaacetic acid) therapy for the removal of inhaled plutonium is the timing of the first injection. This is because DTPA acts on plutonium while it is in the blood, this action is lost after plutonium has been deposited into the organs. It is, therefore, generally accepted that chelation therapy should be started as early as possible after a radiation accident involving plutonium. However, the optimal timing for the first injection of Ca-DTPA is not always apparent. The commencement of Ca-DTPA injection immediately after an accident may be difficult, because of the times it takes between the measurement of the intake of inhaled plutonium into the body and the risk assessment; this measurement must be calculated before the commencement of chelation therapy.

In addition, one of the important factors for controlling efficacy of Ca-DTPA is the chemical form of the inhaled plutonium. Although Ca-DTPA is effective as a compound with the soluble form of plutonium, e.g., nitrate, it has no effect on the insoluble form, e.g., oxide. In fact, we determined in a previous study that Ca-DTPA therapy was not effective at removing plutonium oxide from the lungs or body of rats. Inhalation is not only a possible route of plutonium intake that induces lung tumors but it is furthermore difficult to obtain the effective removal of inhaled plutonium by chelation therapy.

The purpose of the present study is to clarify the effects of Ca-DTPA administration after an initial injection, we also considered the subsequent early period of therapeutic removal of inhaled plutonium nitrate in rats.

MATERIALS AND METHODS

Preparation of the plutonium solution and exposure to plutonium: Plutonium nitric acid solution (0.27N) was prepared for inhalation according to previously reported methods. The activity median aerodynamic diameter of plutonium aerosols was 0.460 µm and the geometric standard deviation was 1.89. Rats were forced to inhale plutonium aerosols through the nose by a method using a radioactive aerosol exposure system designed for rodents.

Ca-DTPA solution: Ca-DTPA solution (dissolved 1g in 5 ml water) was purchased (from Hyle Co., Germany). Before administration, Ca-DTPA was diluted in distilled water to doses of either 30 or 150 µmol/kg. The injection volume of solution per rat was 0.18 ml.

Animals and chelation treatments: Forty male Wistar rats, 3 months of age, weighing an average of 253 g, were used. Before the inhalation of plutonium, all rats were repeatedly set into a retainer for 2 weeks until they became accustomed to exposing their noses through a small hole in order to later inhale the plutonium aerosol without anesthesia. After exposing the rats to plutonium and rinsing their noses, the rats were divided into eight groups of five animals; rats of one group served as the control (G1). Five groups of rats received intraperitoneal injections of Ca-DTPA at a dose of 150 µmol/kg per day for 3 days, beginning at 0.5 (G2), 1(G3), 2(G4), 6(G5) or 12 hr (G6) on day 1, respectively. This dose (150 µmol/kg) is not toxic to rats. One group (G7) received the first injection at the same dose of Ca-DTPA 24 hrs (on day 2) after plutonium inhalation and on day 3 (i.e., two injections of Ca-DTPA). Rats in one group (G8) received Ca-DTPA injected at a dose of 30 µmol/kg for 3 days, beginning at 1hr after inhalation on day 1. This dose is the daily recommended dose of Ca-DTPA for humans, i.e., it is equivalent to 1g per person of 70kg body weight. All rats were kept in separate metabolic cages for the continuous collection of urine and feces for 3 days.

On day 4, all rats were dissected and the lung, nose (airway), trachea, liver, spleen, kidney, muscle, bones, and gastrointestinal tract (without feces) were collected and weighed. The plutonium activity in the pelts was measured but was discounted because of very low or no activity and contamination.

Measurement of plutonium: The whole or circa 1 g of organs, urine, feces, and plasma from each rat was incinerated at 700 °C for 24 hr in a crucible. Two ml of a mixture containing nitric acid, distilled water, and hydrofluoric acid at a ratio of 150: 100: 0.9, were added to the crucible. Subsequently, the solution was poured into a counting vial with scintillator. The alpha activity of plutonium in the vial was measured by an alpha liquid scintillation counter for 30 min. Recovery and counting efficiency were confirmed based on the value measured in the solution with the plutonium by alpha spectrometry; this was done after a comparison was made between an electrodeposited sample made of the same plutonium source as that used in this method and a purchased standard source.
RESULTS

Table 1 shows that the average retention rate from the plutonium intake was 29.4% and the remaining 70.6% was excreted in the feces in the control group (G1). Almost all of the fecal excretion of plutonium took place within day one on all groups. In the G4-G5 and G7-G8 groups, the rates of plutonium retention in the body were lower, whereas the fecal excretion rate was higher than that of the G1-G3 and G6-G7 groups. The urinary excretion rates in the G3-G5 groups were higher than those in G1 and G2 groups, particularly within 24 hr after the first administration of Ca-DTPA.

Table 1  Plutonium activity after inhalation, as excreted in urine and feces for 3 days after inhalation

<table>
<thead>
<tr>
<th>Pu/Group</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>G7</th>
<th>G8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intake of Pu (A)</td>
<td>7257</td>
<td>9056</td>
<td>9160</td>
<td>8787</td>
<td>8547</td>
<td>10514*</td>
<td>8739</td>
<td>11002</td>
</tr>
<tr>
<td>Pu retained in the body(B) (rate/A, %)</td>
<td>(29.4)</td>
<td>(31.9)</td>
<td>(29.2)</td>
<td>(26.0)</td>
<td>(27.5)</td>
<td>(33.0)</td>
<td>(25.1)</td>
<td>(22.9)*</td>
</tr>
<tr>
<td>Pu excreted in the urine (rate/B, %)</td>
<td>35.1</td>
<td>32.0</td>
<td>55.4</td>
<td>51.2</td>
<td>63.5</td>
<td>48.3</td>
<td>54.6</td>
<td>42.6</td>
</tr>
<tr>
<td>(rate/B, %)</td>
<td>(1.23)</td>
<td>(1.17)</td>
<td>(2.14)*</td>
<td>(3.32)*</td>
<td>(2.74)*</td>
<td>(1.43)</td>
<td>(1.62)*</td>
<td>(1.76)*</td>
</tr>
<tr>
<td>Pu excreted in feces (rate/A, %)</td>
<td>7020</td>
<td>6229</td>
<td>6496</td>
<td>6553</td>
<td>6635</td>
<td>7120</td>
<td>6652</td>
<td>8552</td>
</tr>
<tr>
<td>(rate/A, %)</td>
<td>(70.6)</td>
<td>(68.6)</td>
<td>(70.8)</td>
<td>(73.9)</td>
<td>(73.4)</td>
<td>(66.9)</td>
<td>(74.8)</td>
<td>(76.9)</td>
</tr>
</tbody>
</table>

Values are mean ± 1 SE.
*Significantly different from the control; p<0.05 (Wilcoxon signed rank test).

In the group that was administered 30 µmol/kg Ca-DTPA, the lowest rate of retention in the body, the highest fecal excretion rate were observed, at the same time slight higher urinary excretion rate compared to those in G1.

Most of the plutonium retained in the lungs. The rates of retained in the lungs of three groups (G4, 5 and 7) were lower than that of G1. In the measured results of plutonium activity in organs, lower values were found in the liver of G2-G4, G6 and G8; in the bone of G2, G5, G7 and G8, and in the blood of G2-G7, compared to those of G1, respectively.

DISCUSSION

As shown in Table 1, the data obtained from the control group indicated that about 30% of the
plutonium intake deposited in the body, while the remainder (70%) translocated to the gastro-intestinal tract and was excreted in the feces. These results were in correspondence with those in a previous study. In the G3-G5, Ca-DTPA administration was initiated at 1-6 hr after plutonium inhalation. The first injection increased the urinary excretion of plutonium (Fig.1), and resulted in an increase in the excreted amounts of 1.74-2.7 times of that of the G1 group; as observed after a 3-day treatment. However, such changes were not observed in G2, G6, and G7 (Table 1 and Fig. 1). Plutonium concentrations in the liver, bone, and blood of the G2-G5 groups were lower than those of G1. These results indicated that plutonium concentration in serum began to elevate after 0.5 hr - or 1 hr post-inhalation. When the first injection was initiated 1 hr after inhalation, even a 30 µmol/kg dose of Ca-DTPA in G8 took place effects such as a high urinary plutonium excretion, and lower retention rates in the body and liver, compared to both G1 and G3. Therefore, the first Ca-DTPA injection expected to remove plutonium would take place 1-6 hr after plutonium inhalation.

The urinary excretion rate of plutonium by Ca-DTPA was thought to be low, i.e., less than about 1% per day in all groups, as shown in Table 1 and Fig. 1. In a previous study, it was found that the 2-week peritoneal injection of Ca-DTPA at a dose of 150µmol/kg/day to rats, beginning 1hr after intravenous injection of plutonium nitrate reduced plutonium activity to 30% of the control in the skeleton, and to 5% in the liver. The following reasons for differences between two studies were considered. Inhaled plutonium does not easily translocate from lungs to the blood, whereas injected plutonium is able to translocate, thus raising the concentration in the blood. On the other hand, the clearance time of DTPA by intravenous injection is very short: 1.43 min (60% of the injected dose), 4.3 min (20%), and 99 min (20%) in humans. The time to raise Ca-DTPA concentration in the blood is too short to effectively compound with inhaled plutonium. In order to obtain the high efficacy, long-term chelation therapy is required. In conclusion, the present results indicate that initial injection of Ca-DTPA to accelerate the urinary excretion of inhaled-plutonium nitrate should be within 1-6 hr after inhalation.

REFERENCES

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