EFFECTS OF NEW CHELATING AGENT, CBMIDA AND ITS ANALOGUES, ON REMOVAL OF PLUTONIUM IN RATS

Satoshi Fukuda,[1] H. Iida,[1] Y. Xie ,[2] and W. Chen [2]

[1] National Institute of Radiological Sciences, Chiba, Japan
[2] Shanghai Institute of Materia Medica, Shanghai, China.

INTRODUCTION

Chelating agents are important for removal of radionuclides for reduction of the risk of radionuclide-induced cancer. DTPA (diethylenetriaminepentaacetic acid) is, at present, the most effective chelating agent to remove plutonium and other actinides from the human body. However, the development of new chelating agents that are more effective with lower toxicity than DTPA is required for chelation therapy. We developed CBMIDA [catechol-3,6, bis(methyleiminodiacetic acid)] that can remove plutonium especially from bone, more effectively than Ca- and Zn-DTPA (1) and the side effects are lower or similar to those of Zn-DTPA in animals (2). Since CBMIDA was later found to have an untoward action to accumulate Pu in the kidneys, some analogues of CBMIDA were developed. The present study was performed to clarify the effect of CBMIDA and four kinds of analogues on removal of plutonium in rats.

MATERIALS AND METHODS

Thirty male Wistar rats, 3 months of age, were injected intravenously with plutonium (5.6 x 10^3 Bq of ^{239}Pu in 0.12ml of 0.008M sodium citrate solution, pH adjusted to 7.2) after bring anesthetized with a combination of ketamine hydrochloride and xylazine. The plutonium-injected rats were divided into six groups, each consisting of five animals: those receiving

(1) CBMIDA,
(2) N-(4-carboxypheylcarbamoylmenthyl)-N-phosphonomethyl glycine (C-I),
(3) 2-hydroxy-3-(N-phosphonomethyl-N-carboxymethylaminomethyl)-5-carboxy-N-phosphonomethyl-N-carboxymethylbenzenzylamine(C-II),
(4) N-carboxymethyl-N-(carboxypropylcarbamoyl-methyl)-2,3-dihydroxy-5-carbomethoxybenzylamine (C-III),
(5) 2,3-dihydroxy-N,N'-di carboxymethyl-N,N'-di-(o-carboxyphenyl-carbamoylmethyl)-1,4-benzendimethan amine (C-IV) , and
(6) physiological saline.

Each chelating agent was dissolved in distilled water and adjusted to pH 7.2 with sodium bicarbonate to make the solution 0.2 ml against the rat mean body weight of 350 g. Each rat in each group was daily given intraperitoneal injections with a dose of 100 μmol/kg CBMIDA and its analogues for 2 weeks, beginning at 1 hour after plutonium injection on the first day of treatment.

Animals were killed 2 weeks after the plutonium injection. The plasma, bone(femur), liver, kidney, spleen and testis were removed and the plutonium concentration was measured by an alpha liquid scintillation counter.

RESULTS

Table 1 shows the plutonium contents (Bq/g or Bq/ml) of the organs and plasma. There were significant decreases in the bone, liver and testis in the CBMIDA group, compared to those in the control group. There were significant decreases in the bone, liver and spleen in the C-2 group, and the bone and liver in the C-3 group. There was a significant decrease in the bone, and liver but increase in the kidneys in the C-4 group.

There were no significant differences in the body weight of rats before and after the experiment in any group. During the experimental period, no unusual clinical findings were observed. No untoward findings at autopsy were observed.

Table 1 Plutonium content (Bq/g or ml) in the organs and plasma

Group	Femur	Liver	Kidney	Spleen	Testis	Plasma
Control	159.9±15.5	23.0±3.0	15.4±1.3	34.1±7.4	7.8±0.5	4.0±0.1
CBMIDA	71.1±16.6*2	9.5±2.6*1	25.2±5.2	23.1±7.9	4.0±0.6*2	4.6±0.2
C-1	151.2±10.8*1	23.5±1.2	13.2±0.9	23.1±2.8	8.2±1.0	4.0±0.1
C-2	95.5±14.1*1	11.3±1.4*1	12.3±0.9	17.0±2.5*1	6.4±0.6	4.9±0.2
C-3	98.5±14.6*1	11.6±2.0*1	14.4±1.8	18.5±2.5	6.5±1.0	4.6±0.2
C-4	58.4±11.4*2	15.1±2.3	83.0±8.7*3	20.3±3.1	7.9±0.6	4.4±0.2

Values are means ± standard error. Significant difference from control:*1($p<0.05$), *2($p<0.01$).

DISCUSSION

We have demonstrated that CBMIDA can remove plutonium particularly from the bone and liver, which are the target organs, more effectively than Ca-DTPA or Zn-DTPA, either by the injection or oral administration (1, 3), suggesting that the chelating action of CBMIDA is stronger than that of DTPAs. In this experiment, the plutonium content in the bone was also reduced significantly in the CBMIDA group. Because CBMIDA increased the osteoid volume and thickness, its effect to reduce plutonium deposition in bones is attributed to the inhibition of the mineralization of the bone (4). On the other hand, the plutonium content in the kidneys increased, not significantly from that in the control group, and that in the C-4 group increased in the kidneys. These findings indicate that CBMIDA and C-4 can not be used for chelation therapy.

In the C-2 and C-3 groups, the plutonium content was decreased significantly in the bone and liver, and tended to be decreased in the kidneys, spleen and testes. These compounds improved the untoward action of CBMIDA in which the plutonium content increased in the kidneys. No unusual findings were produced by CBMIDA and its analogue groups even at the dose of 100 μmol/kg. All analogues of CBMIDA had the same toxicity as CBMIDA or lower toxicity, but further examination will be necessary on the toxicity, because a dosage of 100 μmol/kg is more than the recommended dose, for example, the daily dose of DTPA for humans is 30 μmol/kg.

In conclusion, the injection of compounds of C-2 and C-3 of CBMIDA analogues effectively removed plutonium from the body. Therefore they should be examined as drugs for chelation therapy in persons contaminated with plutonium.

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