Annals of Nuclear Medicine Vol. 13, No. 2, 127–132, 1999

Technetium-99m complex of *N*-(2-pyridylmethyl)iminodiacetic acid as a new renal radiopharmaceutical

Yoshiharu KARUBE, Koji IWAMOTO and Jiro TAKATA

Faculty of Pharmaceutical Sciences, Fukuoka University

A tetradentate chelating agent constituting of an iminodiacetic acid group and a nitrogen atom of pyridine, *N*-(2-pyridylmethyl)iminodiacetic acid (PMIDA), was coordinated with ^{99m}Tc and evaluated as a renal functional agent. The complex of PMIDA with ^{99m}Tc was prepared by using a stannous chloride solution as a reducing agent. The chelating efficiency was analyzed by thin layer chromatography and electrophoresis. Chelation with ^{99m}Tc resulted in a single radiochemical product. Biological studies were performed in mice and rats. ^{99m}Tc-PMIDA was removed from the circulation solely by the kidneys. Clearance of ^{99m}Tc-PMIDA from the blood and the kidneys was as rapid as that of ^{99m}Tc-diethylenetriaminepentaacetic acid. The rate of blood clearance was unaffected by the administration of probenecid (a test for tubular secretion by the weak-acid mechanism), so that the glomerular filtration rate could be estimated by measuring its clearance from the blood. The results in animals with myohemoglobinuric acute renal failure suggested that ^{99m}Tc-PMIDA might be a useful renal function radiopharmaceutical.

Key words: ^{99m}Tc; *N*-(2-pyridylmethyl)iminodiacetic acid, renal agent, radiopharmaceutical

INTRODUCTION

A NUMBER of radioactive glomerular filtration rate (GFR) agents have been developed and a variety of satisfactory agents are now available, including ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA),[1] ^{169}Yb-DTPA,[2] ^{51}Cr-ethylenediaminetetraacetic acid[3] and ^{125}I-iothalamate.[4] Among those widely used clinically is ^{99m}Tc-DTPA because of the nuclide ^{99m}Tc has such ideal physical properties for imaging and gives a low patient radiation dose per imaginable photon.

DTPA is very stable and also very polar due to the presence of five carboxylic groups and three amino groups. ^{99m}Tc-DTPA routinely obtained by complexation with stannous ion appears to be a single radiochemically pure species, since a variety of radioanalytic separations all yield a single fraction.[5] But values reported for its stability constant range from 10^{17} to 10^{26},[6–8] which lets us suppose that complexes with different structures were involved in the respective preparations. ^{99m}Tc-DTPA has a double negative charge depending on uncoordinated carboxylic groups.[9] The uncoordinated carboxylic groups and amino groups bring the possibility of complicated chelating reactions and ionic plasma protein-binding reaction.[9–13] The chelation of cytosolic ionized calcium ion may produce cell toxicity and ion deregulation in the kidney and bronchus.[14] With a view to finding better renal functional agents with low protein binding and low toxicity, we synthesized many iminodiacetate ligands for ^{99m}Tc and evaluated them as potential renal functional agents.

Davison and coworkers developed a new class of tetradentate N_2S_2 ligands for 1 : 1 chelation with pentavalent Tc.[15] The highly stable chelate of *N*,*N*′-bis(s-benzoylmercaptoacetyl)ethylenediamine with a [Tc = O] core became known as the Tc-DADS complex.[16] In view of this, it is suggested that a tetradentate chelating agent constituted on iminodiacetic acid and nitrogen atom of pyridine, *N*-(2-pyridylmethyl)iminodiacetic acid (PMIDA), also may form a highly stable chelate with ^{99m}Tc. Although the stability constant (4.92) of calcium-PMIDA was lower than that (10.74) of calcium-DTPA,

Received September 9, 1998, revision accepted January 18, 1999.

For reprint contact: Yoshiharu Karube, Ph.D., Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma 8–19–1, Jonan-ku, Fukuoka 814–0180, JAPAN.

E-mail: karube@fukuoka-u.ac.jp

PMIDA was easily complexed with ^{99m}Tc by using stannous ion as the reductant. The present paper is concerned with the *in vivo* behavior of this ^{99m}Tc complex and its relation to chemical structure. The findings show that the PMIDA complex offers a promising new agent as a renal radiopharmaceutical.

MATERIALS AND METHODS

Materials

Technetium-99m pertechnetate ($^{99m}TcO_4^-$) was eluted from a sterile ^{99}Mo-^{99m}Tc shielded generator (Daiichi Radioisotope Laboratories) with isotonic saline. *ortho*-^{131}I-iodohippuran (^{131}I-OIH) was obtained from Daiichi Radioisotope Laboratories. PMIDA was synthesized by the method described previously.[17] PMIDA recrystallized from aqueous ethanol, had m.p. 227–230°C (*Anal.* Calcd for $C_{10}H_{12}N_2O_4$ M.224.2 : C, 53.57; H, 5.39; N, 12.49%. Found: C, 53.31; H, 5.36; N, 12.32). *N*-(Benzyl)-iminodiacetic acid, *N*-(3-pyridylmethyl)iminodiacetic acid and *N*-(4-pyridylmethyl)iminodiacetic acid were synthesized by a similar method. Other materials were purchased from commercial sources.

Formation of ^{99m}Tc complex

A solution containing 0.05 M of PMIDA in 1 m*l* was adjusted to pH 2.0–11.0 with 0.1 M NaOH or 0.1 M HCl. A solution (pH 7.4) containing 0.1 M–0.005 M of PMIDA in 1 m*l* was prepared. A solution (pH 7.4) containing 0.02 M DTPA was also prepared. A 0.1 m*l* of freshly prepared solution (2.0 mg/m*l* in 0.1 M HCl) of stannous chloride (NAKARAI Chemicals Ltd.) was added to the ligand solution and the pH was readjusted to the pH for the purpose (pH 2.0–11.0 or 7.4). The resulting solution was passed through a 0.45 μm membrane filter (Millipore) into a sealed vial. Pertechnetate ($^{99m}TcO_4^-$) (55.5 MBq, 1.0–2.0 m*l*) was added. The mixture was shaken gently and allowed to stand for 10 min at room temperature.

Chemical studies and Physical characteristics of ^{99m}Tc-PMIDA

The efficiency of complexation with ^{99m}Tc was evaluated chromatographically with a 0.25 mm Silica-gel 60 F_{254} plate (E. Merck) developed with an acetonitrile : water (7 : 3) solvent. The purity and charge sign of ^{99m}Tc-PMIDA was determined by paper electrophoresis. Paper strips (Toyo filter paper 51A) were marked at the mid-point before soaking in buffer. The strips were blotted lightly and samples applied to the mid-point from a micropipet, then transferred to the electrophoresis tank and run at a constant voltage of 600 V for 30 min with 0.1 M tris buffer, pH 7.4. The strips were removed after running, and air-dried while mounted on the stiff card to prevent curling.

The TLC plates and paper strips were counted on the images in a gamma camera (Ohio-Nuclear Co.) equipped with a high resolution collimator and a digital computer (VP-450). Movement of paper electrophoresis was determined relative to anionic markers, ^{99m}Tc-DTPA (movement = +4.6 cm) and ^{99m}Tc pertechnetate (movement = +9.0 cm).

The partition coefficient was measured by mixing the ^{99m}Tc-PMIDA with 1 m*l* each of 1-octanol and 0.1 M phosphate buffer (pH 7.0) in a glass tube. This tube was shaken for 20 min at 25°C and then centrifuged at 1500 rpm for 10 min. Two precisely measured samples (0.1 m*l* each) from the 1-octanol and buffer layers were counted in a well-type gamma counter (Packard COBRA II). The partition coefficients were determined by calculating the ratio of the radioactivity of the octanol layer to that of the buffer layer. This measurement was generally repeated three times.

Biodistribution study in mice

The time course of organ distribution was determined in four ICR mice. Each was injected with 0.15 m*l* (2.7 MBq, 0.20 mg) of the ^{99m}Tc-PMIDA through the tail vein. Excretion studies of ^{99m}Tc-DTPA (2.7 MBq, 0.35 mg) and ^{131}I-OIH (1.85 MBq) were also performed for comparison. The mice were killed by collection of blood from the heart at 5, 15, 30 and 60 min after injection. The organs or tissues were removed and weighed. The ^{99m}Tc radioactivity of all organs, blood and urine was counted by images in a gamma camera (Technicare Co.) to measure the radioactivity of the excreted urine and the total radioactivity. The low ^{99m}Tc radioactivity of the blood, liver, spleen and stomach was also counted in a well-type gamma counter. The correction of each count in two measurements was performed by coincidence with the blood radioactivity. The ^{131}I radioactivity was counted in a GM counter. The percentages of the injected dose per organ (ID/organ) were determined by the ratio of organ radioactivity to the total radioactivity. Statistical analysis was performed by Student's t-test for unpaired data.

Imaging study in mice and rats

The gamma camera was a SIGMA 420, a 37 tube array of 50.8 mm bialkali PMTs coupled to a 33.6 cm diameter by 0.63 cm thick NaI (Tl) Scintillation crystal with a patient applied for Ohio-Nuclear electronic and optical techniques for ultra high resolution. Its field of view is a hexagon that is 24.8 cm across the flats.

Mice or rats were injected through the tail vein with 0.15 m*l* (2.7 MBq, 0.0009 mmol) of ^{99m}Tc-PMIDA or ^{99m}Tc-DTPA for imaging studies. Images of four mice or rats were obtained with a gamma camera (SIGMA 420) equipped with a high resolution collimator (Model 14S17033 High Sensitivity parallel hole) in the fixed position of the mice and were collected with a digital computer (Vip-450). The software was Vip-450F V5.0 System. The total count in each scintigram frame was 5×10^4.

Blood disappearance rates

Three male Wistar rats weighing 350 ± 20 g were used in the experiment. Each animal was anesthetized with 25 mg/kg of sodium pentobarbital intraperitoneally. A catheter with three necks was placed in a femoral vein for injection of ^{99m}Tc complex and isotonic saline or probenecid infusion. They were placed under a gamma camera provided with digital storage (VP-450). Following infusion of isotonic saline at the rate of 20 μl/min, 90 min, digital images were acquired in the anterior projection simultaneously with a bolus injection of ^{99m}Tc-PMIDA (7.4 MBq) or ^{99m}Tc-DTPA (7.4 MBq). Rapid (10 sec) serial digital images were acquired for 24 min and were used to quantitatively estimate blood clearance by the disappearance of radioactivity in the heart. After infusion of 50 mg/kg/hr probenecid[18,19] at the rate of 20 ml/min, 90 min in the same animal, ^{99m}Tc-PMIDA (7.4 MBq) or ^{99m}Tc-DTPA (7.4 MBq) was injected and measured as above.

For blood studies of ^{131}I-OIH, a catheter was placed in a femoral vein for tracer injection and saline or probenecid infusion, and another was placed in a femoral artery for blood sampling. Following infusion of saline at the rate 20 μl/min, 90 min, 1.85 MBq of OIH was injected, and 0.1–0.2 m*l* samples of blood were taken at 1, 5, 10, 15 and 20 min after the injection. After infusion of 50 mg/kg/hr probenecid at the rate of 20 μl/min, 90 min in the same animal, 1.85 MBq of OIH was injected and the effect of the administration of probenecid on the rate of blood clearance was investigated. The blood samples were counted in a well-type gamma counter. The correction of each radioactivity between ^{99m}Tc and ^{131}I was performed by coincidence with the radioactivity at 1 min.

The rate constant of blood clearance was calculated from ^{99m}Tc radioactivity or ^{131}I radioactivity from 5 min to 20 min.

Glycerol-induced acute renal failure

Myohemoglobinuric acute renal failure in four mice[20] was induced by the injection of 50% glycerol (1 m*l*/100 g) into the muscles of the left hind limb. One day after the glycerol injection, mice showed signs of marked oliguria and ^{99m}Tc complex solution was injected. The kidney time activity curves and cumulative percent dose in the bladder was investigated by means of a gamma camera with digital storage.

Distribution of radioactivity in blood

^{99m}Tc-PMIDA complex was injected into the rat through the tail vein. The blood was collected in a heparinized syringe at 1 hr after the injection. One m*l* of the blood was mixed slowly with 6 m*l* of saline solution. The mixture was layered on the top of 3 m*l* of Conray 400-Ficoll solution and centrifuged at 400 × *g* (1550 rpm) for 30 min. Each fraction was separated and the radioactivity measured with a well-type gamma counter.

Table 1 The effect of pH and PMIDA concentration on ^{99m}Tc labeling

Concentration of PMIDA	pH	Yield (%)
0.05 M	11.0	32.0 ± 2.6
0.05 M	10.0	72.3 ± 3.6
0.05 M	9.0	89.6 ± 1.7
0.05 M	8.0	99.6 ± 0.1
0.05 M	7.0	99.2 ± 0.1
0.05 M	6.0	99.8 ± 0.1
0.05 M	5.0	99.7 ± 0.1
0.05 M	4.0	99.6 ± 0.1
0.05 M	3.0	98.6 ± 0.1
0.05 M	2.0	88.8 ± 2.8
0.1 M	7.4	99.6 ± 0.2
0.05 M	7.4	99.7 ± 0.2
0.04 M	7.4	99.7 ± 0.1
0.03 M	7.4	99.7 ± 0.1
0.02 M	7.4	99.7 ± 0.1
0.01 M	7.4	99.7 ± 0.1
0.005 M	7.4	99.4 ± 0.4

Measurement of in vivo *plasma protein binding*

^{99m}Tc-PMIDA or ^{99m}Tc-DTPA was injected through the tail vein into each three mice. The blood was collected in a heparinized syringe at 30 min and 1 hr after the injection. Heparinized blood samples were centrifuged and the cells were removed. The method for measuring protein binding was gel filtration with a PD-10 column prepacked with Sephadex G-25.[11] A 0.05 m*l* sample of the serum was applied to the PD-10 column and eluted with saline. Each 0.2 m*l* fraction was put into separate tubes and counted in a well-type gamma counter.

Toxicity study

The acute toxicity of PMIDA and DTPA were determined in five male ICR mice weighing 30 ± 2 g each. PMIDA and DTPA were dissolved in saline and the pH of these solutions was adjusted to 7.4 with 0.1 M NaOH. A dose of 1 g/kg 0.05–0.1 M solution of ligand was administered intravenously to each mouse. The mice were followed up for 30 days with normal animal care.

RESULTS

Chemical studies

The ^{99m}Tc complex of PMIDA showed a sharp single peak, the Rf value for which fell to 0.40 with 70% acetonitrile. In this solvent pertechnetate gave an Rf value of 0.98, and reduced hydrolyzed ^{99m}Tc remained at the origin. Table 1 shows the yields of ^{99m}Tc labeling for the various concentrations of PMIDA and the various pH. As judged by the chromatography, PMIDA was complexed with ^{99m}Tc in a yield constantly greater than 99% in the pH range 3.0–8.0. PMIDA was soluble in acidic and neutral aqueous media and rarely formed precipitates or colloid with Sn in the pH range 4.0–7.5. The same chromatogram

Table 2 Biodistribution of radioactivity in mice

Biodistribution data of ^{99m}Tc-PMIDA*

Organ	5 min	15 min	30 min	1 hr
Urine	42.77 ± 3.10	66.01 ± 2.75	84.06 ± 1.99	93.27 ± 0.89
Kidneys	6.84 ± 1.28	2.47 ± 0.53	1.27 ± 0.20	0.76 ± 0.25
Blood**	12.57 ± 0.87	6.05 ± 0.55	1.70 ± 0.27	0.59 ± 0.14
Liver	2.62 ± 0.43	1.73 ± 0.24	0.84 ± 0.14	0.46 ± 0.11
Intestines	3.75 ± 0.65	1.93 ± 0.35	0.81 ± 0.23	0.56 ± 0.11
Spleen	0.12 ± 0.02	0.08 ± 0.02	0.04 ± 0.01	0.03 ± 0.01
Stomach	0.49 ± 0.11	0.28 ± 0.05	0.15 ± 0.06	0.05 ± 0.01

Biodistribution data of ^{131}I-OIH*

Organ	5 min	15 min	30 min	1 hr
Urine	74.88 ± 1.11	92.56 ± 1.14	96.85 ± 2.21	97.07 ± 0.54
Kidneys	7.25 ± 0.10	1.99 ± 1.24	0.75 ± 0.23	0.70 ± 0.38
Blood**	6.99 ± 1.36	1.25 ± 0.50	0.47 ± 0.27	0.27 ± 0.05
Liver	2.99 ± 0.56	0.90 ± 0.13	0.43 ± 0.24	0.30 ± 0.01
Intestines	0.82 ± 0.11	0.51 ± 0.10	0.36 ± 0.19	0.12 ± 0.02
Stomach	0.59 ± 0.08	0.28 ± 0.04	0.24 ± 0.09	0.22 ± 0.05

Biodistribution data of ^{99m}Tc-DTPA*

Organ	5 min	15 min	30 min	1 hr
Urine	42.56 ± 2.98	65.89 ± 2.75	83.46 ± 3.57	93.78 ± 0.80
Kidneys	7.35 ± 0.58	2.91 ± 0.70	1.33 ± 0.55	1.00 ± 0.21
Blood**	12.59 ± 0.70	6.03 ± 0.18	1.78 ± 0.46	0.59 ± 0.15
Liver	2.55 ± 0.14	1.65 ± 0.15	0.70 ± 0.14	0.50 ± 0.15
Intestines	1.78 ± 0.31	0.89 ± 0.11	0.55 ± 0.10	0.11 ± 0.08
Stomach	0.52 ± 0.12	0.31 ± 0.08	0.10 ± 0.05	0.05 ± 0.01

* Values are percent injected dose, mean ± S.D. for four mice at each time after injection.
** Blood was assumed to account for 7.78% of total body mass.

was obtained even after the product had stood for 24 hr at room temperature. On the other hand, the ^{99m}Tc labeling of *N*-(benzyl)iminodiacetic acid, *N*-(3-pyridylmethyl)-iminodiacetic acid and *N*-(4-pyridylmethyl)iminodiacetic acid did not give a sharp single peak.

Electrophoresis of ^{99m}Tc-PMIDA on paper strips showed a single species which migrated about 1.2 cm toward the anode, indicating a slightly negative-charged species. In a control of hydrolyzed ^{99m}Tc there was no migration under the conditions of the experiment. Under the same conditions, ^{99m}Tc-DTPA and pertechnetate migrated about 4.6 cm and 9.0 cm toward the anode, respectively.

The logarithm of the octanol/water partition coefficients of the ^{99m}Tc complexes can be used to predict the relative urinary/hepatobiliary clearance of the complex.[21] We selected ^{99m}Tc-E-HIDA complex as a lipophilic control complex. The log *P* (the radioactivity of octanol/the radioactivity of water) of ^{99m}Tc-PMIDA, ^{99m}Tc-DTPA and ^{99m}Tc-E-HIDA were −4.0, −5.0 and −1.2, respectively. ^{99m}Tc-PMIDA was a more hydrophilic complex than ^{99m}Tc-E-HIDA.

In vivo *distribution studies*

Table 2 shows the organ distribution of ^{99m}Tc-PMIDA in mice from 5 min to 1 hr. Organ distributions indicated clearance by the kidneys. The initial radioactivity of the liver and intestines is due to residual blood. The values at 30 min were 84% of the injected dose in the urine for ^{99m}Tc-PMIDA, 97% for OIH and 84% for ^{99m}Tc-DTPA. The difference between ^{99m}Tc-PMIDA and OIH was significant ($p < 0.01$), but the difference between ^{99m}Tc-PMIDA and ^{99m}Tc-DTPA was not. Typical scintigrams (Fig. 1) from the rats revealed that the ^{99m}Tc complex was rapidly excreted in urine, and provided excellent renal images with no significant extrarenal background.

Figure 2 shows the time-activity curves for the heart in rats administered ^{99m}Tc-PMIDA, ^{99m}Tc-DTPA or ^{131}I-OIH. The disappearance of ^{99m}Tc radioactivity from the blood ($t_{1/2} = 11.7 \pm 0.6$ min) was almost same as that of ^{99m}Tc-DTPA ($t_{1/2} = 11.8 \pm 0.5$ min) and lower than that of ^{131}I-OIH ($t_{1/2} = 9.9 \pm 0.5$ min). The rate of blood clearance of ^{99m}Tc-PMIDA and ^{99m}Tc-DTPA was unaffected by the administration of probenecid used as a test for tubular secretion by the weak-acid mechanism. On the other hand the rate ($t_{1/2} = 13.6 \pm 0.6$ min) of blood clearance for ^{131}I-

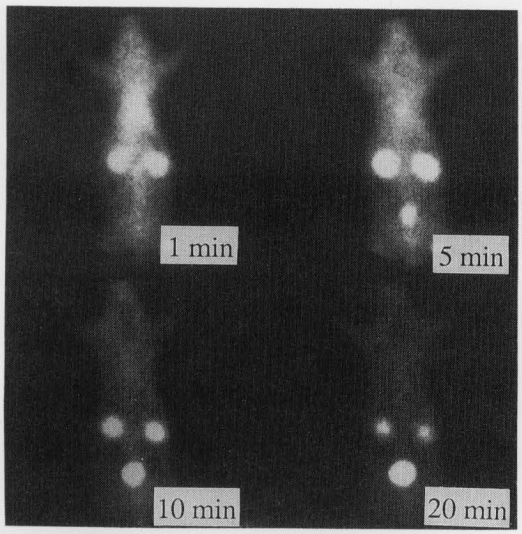

Fig. 1 Scintigrams obtained with ^{99m}Tc-PMIDA after the administration to a rat (anterior projection).

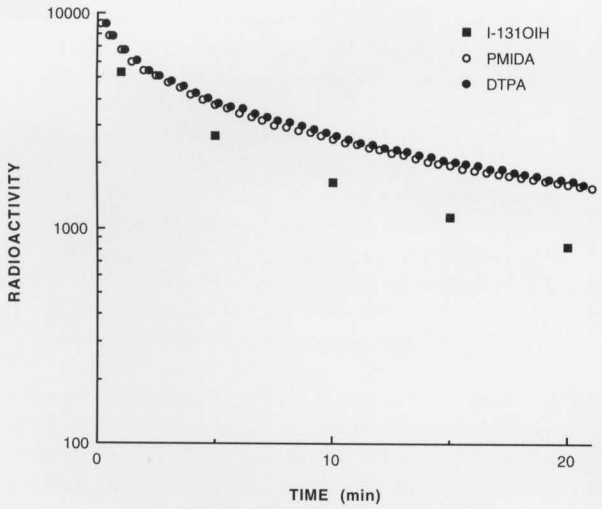

Fig. 2 Time-activity curves for the heart in rat administered ^{99m}Tc-PMIDA, ^{99m}Tc-DTPA, or ^{131}I-OIH.

OIH was decreased by the administration of probenecid.

Figure 3 shows the time-activity curves for the kidneys and cumulative percent dose in the bladder in mice with myohemoglobinuric acute renal failure. The time-activity curves for the kidneys became slightly abnormal and the cumulative percent dose in the bladder was decreased.

Radioactivity in blood

The main radioactivity (95.27%) was found in blood plasma. The radioactivity of blood corpuscle fractions was almost completely removed in the wash.

When the serum sample was gel-chromatographed on a PD-10 column, plasma protein was found in fractions 17 to 23, ^{99m}Tc-PMIDA in fractions 26 to 58 and ^{99m}Tc-DTPA in fractions 25 to 55. ^{99m}Tc-DTPA had the propensity to bind to plasma protein, 3.6 ± 0.6% at 30 min and

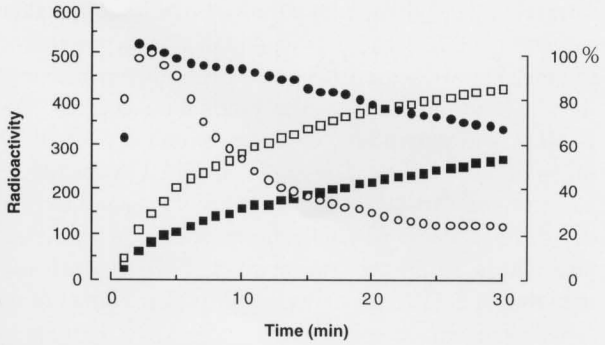

Fig. 3 Kidney time-activity curves and cumulative percent dose in bladder in mice administered ^{99m}Tc-PMIDA.
□ control-bladder ■ glycerol-bladder
○ control-kidney ● glycerol-kidney

12.8 ± 3.0% at 1 hr. ^{99m}Tc-PMIDA was only bound to plasma protein, 1.4 ± 0.2% at 30 min and 3.2 ± 0.5% at 1 hr.

Toxicity

Toxicity has shown the minimum lethal dose of the intravenously injected PMIDA to be 60 mg/kg in mice. On the other hand, the minimum lethal dose of injected DTPA was 30 mg/kg. In the toxicity study, no animal died during the period at a dose lower than 55 mg/kg of PMIDA. No significant differences in body weight were observed between the tested animals and the controls during the 30 days after administration.

DISCUSSION

PMIDA, a tetradentate chelating agent, formed a stable chelate with reduced ^{99m}Tc. PMIDA was soluble in aqueous media and was labeled with ^{99m}Tc in high yield by a simple procedure. A single uniform complex was obtained over a wide pH range of the solution. These properties are favorable to kit preparation.

The lipophilicity of the complex must also be kept within certain limits to minimize the degree of hepatobiliary excretion of the complex. ^{99m}Tc-PMIDA is more hydrophilic than ^{99m}Tc-E-HIDA. This characteristic is essential in an ideal agent for measuring GFR.

The ^{99m}Tc labeling of *N*-(benzyl)iminodiacetic acid, *N*-(3-pyridylmethyl)iminodiacetic acid and *N*-(4-pyridylmethyl)iminodiacetic acid did not give a sharp single peak. On the other hand, ^{99m}Tc labeling of PMIDA gave a sharp single peak. In an attempt to explain the relationship between the ligand structures, these results show that the PMIDA : Tc ratio in the complex is 1 : 1 and not 2 : 1. The position of the pyridine nitrogen atom and the iminodiacetate group on the PMIDA ligand may play an important role in this complex. It seems that the coordination sphere includes two nitrogens and two oxygens of these carboxylates.

Agents excreted by glomerular filtration must be freely

filterable by the glomerular ultrafilter. The ideal agent for measuring GFR must not be bound to plasma proteins or to other blood components either reversibly or irreversibly.[22] Plasma analysis by gel filtration showed that ^{99m}Tc-PMIDA was only bound to plasma proteins 1.4% at 30 min and 3.2% at 1 hr. Though ^{99m}Tc-PMIDA seen to be superior to ^{99m}Tc-DTPA in the results of plasma analysis, this difference was within the limits of error in results for distribution. As the chelating ability of PMIDA was lower than that of DTPA, we expected PMIDA to impair renal function much less.

^{99m}Tc-PMIDA has excellent renal excretion characteristics, as confirmed by the organ distribution studies in animals. Scintigraphic study of ^{99m}Tc-PMIDA suggests its potential utility for assessment of the renal system. The rate of blood clearance was unaffected by the administration of probenecid used as a test for tubular secretion by the weak-acid mechanism. This result shows that ^{99m}Tc-PMIDA is not actively or passively reabsorbed or secreted by the renal tubular epithelium.

The results for animals with acute myohemoglobinuric renal failure suggest that ^{99m}Tc-PMIDA may be a useful renal function radiopharmaceutical. These results are quite satisfactory for a renal functional agent.

ACKNOWLEDGMENT

This work was supported in part by funds from the Central Research Institute of Fukuoka University.

REFERENCES

1. Richards P, Atkins HL. Technetium-99m-labeled compounds. *J Nucl Med* 7: 165–170, 1967.
2. Hosain F, Reba RC, Wagner Jr HN. Measurement of glomerular filtration rate using chelated ytterbium-169. *Int J Appl Radiat Isot* 20: 517–521, 1969.
3. Bianchi C. Measurement of the glomerular filtration rate. *Progr Nucl Med* 2: 21–53, 1972.
4. Skov PE. Glomerular filtration rate in patients with severe and very severe renal insufficiency. Determined by simultaneous inulin, creatinine and I-125-iothalamate clearance. *Acta Med Scand* 187: 419–428, 1970.
5. Russell CD, Speiser AG. Iminodiacetate complexes of technetium: An electrochemical study. *Int J Appl Radiat Isot* 33: 903–906, 1982.
6. Agha N, Persson RBR. Comparative labelling and biokinetic studies of ^{99m}Tc-EDTA (Sn) and ^{99m}Tc-DTPA (Sn). *J Nucl Med* 16: 30–35, 1977.
7. Dewanjee MK, Brueggeman PM. Dissociation constants of Tc-99m chelates with serum protein. *J Nucl Med* 18: 625, 1977.
8. Levin VI, Gracheva MA, Ilyushchenko ON. The stability constant of ^{99m}Tc-DTPA complex. *Int J Appl Radiat Isot* 31: 382–385, 1980.
9. Russell CD, Crittenden RC, Cash AG. Determination of net ionic charge on Tc-99m-DTPA and Tc-99m-EDTA by a column ion-exchange method. *J Nucl Med* 21: 354–360, 1980.
10. Hauser W, Atkins HL, Nelson KG, Richard P. Technetium-99m-DTPA: A new radiopharmaceutical for brain and kidney scanning. *Radiology* 94: 679–684, 1970.
11. Russell CD, Bischoff PG, Rowell KL, Kontzen F, Lloyd LK, Tauxe WN, et al. Quality control of Tc-99m DTPA for measurement of glomerular filtration. *J Nucl Med* 24: 722–727, 1983.
12. Carlsen JE, Mu'ller ML, Lund JO, Trap-Jensen J. Comparison of four commercial Tc-99m (Sn)-DTPA preparations used for the measurement of glomerular filtration rate. *J Nucl Med* 21: 126–129, 1980.
13. Noll B, Seifert S, Munze R. Preparation and characterization of technetium (IV) complexes with diethylenetriaminepentaacetic acid and ethylenediaminetetraacetic acid as ligands. *Int J Appl Radiat Isot* 34: 581–584, 1983.
14. Trump BF, Berezesky IK, Smith MW, Phelps PC, Elliget KA. The relationship between cellular ion deregulation and acute and chronic toxicity. *Toxicol Appl Pharmacol* 97: 6–22, 1989.
15. Davison A, Sohn M, Orvig C, Jones AG, LaTegola MR. A tetradentate ligand designed specifically to coordinate technetiumn. *J Nucl Med* 20: 641, 1979.
16. Davison A, Jones AG, Orvig C, Sohn M. A new class of oxotechnetium (5+) chelate complexes containing a $TcON_2S_2$ core. *Inorg Chem* 20: 1629–1632, 1980.
17. Irving H, DaSilva JJRF. Metal complexes of *N*-(2-pyridylmethyl)iminodiacetic acid. *J Chem Soc* 1963: 945–952, 1963.
18. Fritzberg AR, Kashima S, Eshima D, Johnson DL. Synthesis and biological evaluation of technetium-99m MAG3 as a hippuran replacement. *J Nucl Med* 27: 111–116, 1986.
19. Klopper JF, Hauser W, Atkins HL, Eckelman WC, Richards P. Evaluation of ^{99m}Tc-DTPA for the measurement of glomerular filtration rate. *J Nucl Med* 13: 107–110, 1972.
20. Ayer G, Grandchamp A, Wyler T, Truniger B. Intrarenal hemodynamics in glycerol-induced myohemoglobinuric acute renal failure in the rat. *Circulation Research* 29: 128–135, 1971.
21. Burns HD, Worley P, Wagner Jr HN, Marzilli L, Risch V. Design of technetium radiopharmaceuticals. *In* The Chemistry of Radiopharmaceuticals. Heindel ND, Burns HD, Honda T, Brady LW (eds.), New York, Masson Publishing USA, Inc., pp. 269–289, 1978.
22. Russell CD. Radiopharmaceuticals used to assess kidney function and structure. *In* Nuclear Medicine in Clinical Urology and Nephrology. Tauxe WN, Dubovsky EV (eds.), Appleton-Century-Crofts, Norwalk, Connecticut, pp. 7–29, 1985.