A Comparison of Biodistribution between ^{111}In -DTPA Octreotide and ^{111}In -DOTATOC in Rats Bearing Pancreatic Tumors

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ABSTRACT. ^{111}In -DTPA octreotide (DTPAOC) has been used for detecting somatostatin receptor positive tumor for years. ^{111}In -DOTA-Tyr3-octreotide (DOTATOC) is newly developed for diagnostic and therapeutic purposes. In this study, we compared the biodistribution and tumor uptake ratio after injection of ^{111}In -DTPAOC and ^{111}In -DOTATOC in rats. Twelve rats bearing pancreatic tumors were divided into two groups: six rats were sacrificed at 4 hr after injection of 3.7 MBq of ^{111}In -DTPAOC and another 6 rats were sacrificed at the same time after injection of 3.7 MBq of ^{111}In -DOTATOC. Samples of various organs were obtained and counted to calculate the tissue concentration. In addition, 12 rats bearing pancreatic tumors were scanned at 4, 24, and 48 hr after injection of 37 MBq of ^{111}In -DTPAOC or ^{111}In -DOTATOC. The tumor uptake ratios (T/N ratio) were calculated. The biodistribution data showed that the activity in the tumor as well as in the kidney was significantly higher in the ^{111}In -DOTATOC group than in the ^{111}In -DTPAOC group, although both radiopharmaceuticals had the expected high affinity to the tumor. The T/N ratios in the ^{111}In -DOTATOC group were also significantly higher than those in the ^{111}In -DTPAOC group at 24 hr after injection. We conclude that ^{111}In -DOTATOC showed lower clearance than ^{111}In -DTPAOC in the rats bearing pancreatic tumors, although both of these radiopharmaceuticals showed expected high tumor uptake.

KEY WORDS: ^{111}In -DOTATOC, ^{111}In -DTPA Octreotide, pancreatic tumor, rat.

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Somatostatin receptors (SSTR) have been identified in different kinds of tumors such as neuroendocrine tumors, and tumors of the central nervous system [22] breast [5] lung and lymphatic tissue [18]. Endogenous somatostatin is easily attacked by aminopeptidase or endopeptidase, and hence has a very short biologic half-life (<2 min); thus, somatostatin itself cannot be used as an imaging agent in nuclear medicine. The commercially available somatostatin (SST) analog Octreotide [(D)Phe-Cys-Phe-(D) Try-Lys-Thr-Cys-Thr] has been shown to be effective in controlling the growth of some human tumors. ^{111}In -DTPA octreotide (^{111}In -DTPAOC) is a radiopharmaceutical that binds to somatostatin receptors, and is used for scintigraphic imaging of the previously mentioned tumor types [13, 14, 26]. ^{111}In -DTPAOC has also been reported to be able to detect neuroendocrine tumor such as insulinoma in dogs [9, 24]. In the study by Robben *et al.*, they concluded that ^{111}In -DTPAOC SPECT appeared as effective as Ultrasonography and Computed Tomography in detecting insulinomas [24]. Accurate localization of the tumors is very important for a successful surgery.

A new and fascinating application is the use of labelled octreotide for radionuclide therapy. For therapeutic purposes, yttrium-90 (^{90}Y) is considered one of the best radionuclides due to its favorable physical and chemical

characteristics [3]. However, ^{90}Y -DTPAOC is not stable, resulting in haematopoietic toxicity *in vivo* as ^{90}Y is released from the complex and taken up in the skeleton [12, 25].

Recently, a newly developed somatostatin analogue, DOTA-Tyr3-octreotide, named DOTATOC, has shown favorable characteristics for both diagnosis and therapy: high affinity for somatostatin receptors [11, 16], high hydrophilicity [2] and ease of labeling and stability with ^{111}In and with ^{90}Y [4, 19, 20, 27].

Although DOTATOC has been proven to have a high affinity for neuroendocrine tumors, there have been few direct comparative studies of ^{111}In -DTPAOC and ^{111}In -DOTATOC (15, 18). In this study, we compared the biodistribution data and tumor uptake ratios between ^{111}In -DTPA octreotide and ^{111}In -DOTATOC in rats with pancreatic tumors.

MATERIALS AND METHODS

Experimental animals: Twenty-four Lewis male rats (200–250 g) were used in the experiment. All rats were housed in a room maintained at a constant temperature (25°C) and with a 12:12 hr light-dark cycle. Food and water were given *ad libitum*. This study was approved by the local Institutional Review Board according to the Helsinki recommendations and internationally accepted principles for the care and use of experimental animals. The animal care and laboratory procedure were also approved by The Institu-

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tional Animal Care and Use Committee of National Chung Hsing University and Taichung Veterans General Hospital.

Materials: $^{111}\text{InCl}_3$ was obtained from Mallinckrodt Medical (Petten, The Netherlands). DTPAOC and DOTATOC were synthesized by INER (Institute of Nuclear Energy Research, Taoyuan, Taiwan). The purity and structural identification were analyzed by high-performance liquid chromatography (HPLC) and mass spectrometry separately. All other chemicals were obtained from commercial sources.

Preparation of ^{111}In -DTPA octreotide and ^{111}In -DOTATOC: The composition of the INER DTPAOC kit and its radiolabeling method were performed following the instructions for the preparation of ^{111}In DTPAOC provided by Mallinckrodt. The preparation of ^{111}In -DOTATOC followed the procedure described previously [19, 20]. Briefly, 20 μg of DOTATOC were dissolved in 50 μl sodium acetate buffer (0.4 M, pH 5.5) with 1 mg gentisic acid; after the addition of 6 mCi $^{111}\text{InCl}_3$ (0.05 M HCl), the solution was heated at 90°C for 25 min. Quality control was obtained with the use of Sep-Pak C18 cartridge and HPLC as previously described [19]. The radiochemical purities of ^{111}In -DOTATOC and ^{111}In -DTPAOC were more than 95%.

Tumor cell line culture: AR4-2J tumor cells (American Type Culture Collection, Manassas, VA, U.S.A.) were used for tumor implantation. The tumors were routinely cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS), 2 mM L-glutamine, 50 units/ml penicillin, and 50 $\mu\text{g}/\text{ml}$ streptomycin. After they had grown exponentially for one week, a concentration of approximately 4×10^7 cells per ml was established. The cell viability was over 90%, as determined by trypan-blue exclusion.

Inoculation of tumor: Using a 27 gauge needle, a AR4-2J tumor cell suspension, containing 4×10^6 cells in a volume of 0.1 ml, was injected subcutaneously into the left thigh of each rat. The puncture site was gently compressed, using cotton gauze, for 15 sec to prevent bleeding. Two weeks after inoculation, tumor growth was checked by visualization and palpation.

Biodistribution: Twelve male Lewis rats bearing AR4-2J tumor cells were divided into two groups. The six rats in Group 1 were sacrificed at 4 hr after injection of approximately 3.7 MBq of ^{111}In -DTPAOC via the tail veins. The six rats in Group 2 were injected with 3.7 MBq of ^{111}In DOTATOC in a procedure similar to the one described above. Samples of tumor, normal liver, lung, kidney, spleen, muscle, bone, small intestine and whole blood (1 ml) were taken and weighed carefully. The counts of radioactivity were measured by a gamma counter and tissue concentrations were calculated and expressed as percent injected dose per gram (% ID/g).

Imaging: Twelve rats bearing pancreatic tumors were divided into two groups (6 in each group). After injection with 37 MBq of ^{111}In DTPAOC or ^{111}In DOTATOC, the rats were anaesthetized with pentobarbital (0.45 ml/kg body weight). The rats were placed in the prone position under

the camera with the legs stretched out and fixed. Planar posterior views of the legs with total counts of 300 K were obtained at 4, 24, and 48 hr after administration of the radioactive agents using a large field-of-view gamma-camera (Elsint APEX 415 W) with an APC-3 (low energy, medium resolution, medium sensitivity) collimator. The images were obtained in a 256×256 matrix.

Calculation of tumor uptake ratio: For determination of radioactivity in the tumor on the images, regions of interests (ROIs) were drawn over the tumor and normal soft tissue on the other thigh. The formula used to calculate the tumor uptake ratio (T/N ratio) for the ROIs of each rat is shown below:

$$\text{T/N ratio} = \frac{\text{Mean counts of ROI1}}{\text{Mean counts of ROI2}}$$

Where

ROI1 = ROI over the tumor

ROI2 = ROI over soft tissue on the normal thigh

The T/N ratio was taken as an index of the ability of the radiopharmaceutical to localize the tumor.

Statistical Analysis: Statistical analysis of the results was made with the Statistica for Windows Release 4.5 package (StatSoft, Inc., Statistica, OK, U.S.A.) using Mann-Whitney *U* tests. Results are expressed as mean $\pm$ standard deviation (SD). A *p* value less than 0.05 was considered statistically significant.

RESULTS

The results of the biodistribution study of rats with pancreatic cancer, expressed as % ID/g of tissue, are summarized in Table 1. Our data show that the radioactivity in both the tumor and kidney was high at 4 hr post-injection of In-111 DTPAOC or In-111 DOTATOC. The activity in the tumor as well as in the kidney was significantly higher in the In-111 DOTATOC group than in the In-111 DTPAOC group. The concentrations of radioactivity in other organs such as normal liver, lung, muscle, spleen, bone, small intestine and whole blood were quite low.

The T/N ratios in the rats with pancreatic tumors are shown in Table 2. In the In-111 DTPAOC group, the mean T/N ratio was as high as 24.21 at 4 hr after injection, declined to 17.88 at 24 hr and 9.04 at 48 hr. In the In-111 DOTATOC group, the T/N ratio was as high as 26.12 at 4 hr after injection, declined to 21.5 at 24 hr and 17.12 at 48 hr. The uptake of In-111 DTPAOC and In-111 DOTATOC was easily identified throughout the study (Figs. 1-2). The T/N ratios showed no statistical difference between the In-111 DTPAOC and In-111 DOTATOC groups at both 4 hr and 24 hr after injection. However, the T/N ratio in the In-111 DOTATOC group was statistically higher than that in the DTPAOC group at 48 hr after injection.

DISCUSSION

Peptide receptor-mediated radionuclide therapy has been

Table 1. Tissue distributions in rats with pancreatic tumors at 4 hr after injection of In-111 DTPAOC or In-111 DOTATOC

Organ Tissue	Biodistribution (%ID/g or mI)	
	In-111 DTPAOC	In-111 DOTATOC
Tumor*	2.039 ± 0.876	6.934 ± 2.788
Blood	0.043 ± 0.003	0.048 ± 0.012
Muscle*	0.010 ± 0.005	0.027 ± 0.008
Liver	0.378 ± 0.103	0.465 ± 0.101
Spleen	0.574 ± 0.273	0.571 ± 0.058
Lung*	0.144 ± 0.018	0.316 ± 0.102
Small intestine	0.311 ± 0.061	0.212 ± 0.017
Bone*	0.019 ± 0.007	0.198 ± 0.075
Kidney*	3.345 ± 0.642	6.875 ± 1.357

Note: n=6, mean ± standard deviation (SD); * $p < 0.05$

Table 2. The ratio of radiotracer uptake between tumor and normal tissue after intravenous injection of In-111 DTPAOC or In-111 DOTATOC

Radiopharmaceuticals	T/N Ratio		
	4 hr	24 hr	48 hr*
In-111 DTPAOC	24.21 ± 8.77	17.88 ± 5.55	9.04 ± 3.83
In-111 DOTATOC	26.12 ± 11.03	21.50 ± 9.63	17.12 ± 8.03

Note: n=6, mean ± standard deviation (SD); * $p < 0.05$.

Fig. 1. Dorsal view of a rat bearing a pancreatic tumor over the left thigh. The uptake of In-111 DTPAOC in the tumor is significantly high (arrows). The high radioactivity in the abdomen is mainly due to the uptake in the kidneys. The uptake of In-111 DTPAOC in other organs is low.

used for several years in the treatment of progressive, metastasized somatostatin receptor-positive tumors [15, 20, 29]. Although In-111 DTPAOC can be used as a therapeutic agent based on In-111's emission of Auger and conversion electrons, beta-emitting radionuclides such as Y-90 may be even more effective than In-111 for peptide receptor radionuclide therapy. Unfortunately, the stability of Y-90 DTPAOC is not good, and it is unsatisfactory for clinically therapeutic usage. DOTA is a chelator that ensures high *in*

vivo stability when labeling with Y-90. Y-90 DOTATOC has been reported to be valuable in the treatment of somatostatin-positive tumors [4, 27]. In this study, we directly compared the biodistribution of In-111 DTPAOC and In-111 DOTATOC in rats bearing pancreatic tumors.

The cell line, AR4-2J, used in this study was derived from rat pancreas tumor known to express high levels of somatostatin type-2 receptors (STTR2) [8]. With this model, high clinical relevance can be expected because SSTR2 is

Fig. 2. Dorsal view of a rat bearing a pancreatic tumor over the left thigh. The uptake of In-111 DOTATOC in the tumor is significantly high (arrows). The high radioactivity in the abdomen is mainly due to the uptake in the kidneys. The uptake of In-111 DOTATOC in other organs is low.

the most abundant of the 5 SSTRs in human SSTR-expressing tumors [23]. It has also been reported that humans and rats share a 95% SSTR2 sequence homology [23]. In our study, In-111 DOTATOC showed significantly higher uptake than In-111 DTPAOC in the pancreatic tumor 4 hr after injection of radiotracer, although In-111 DTPAOC also showed the expected high tumor uptake. The T/N ratios from scintigraphic images were significantly higher in the In-111 DOTATOC group than that in the In-111 DTPAOC group at 48 hr after injection although the difference was not significantly on the early 4 hr and 24 hr images. This indicated that In-111 DOTATOC eliminated more slowly in the pancreatic tumor than In-111 DTPAOC in rats. Our data were similar to those of previous studies [7, 23]. Reubi *et al.* reported that DOTATOC labeled with various three-fold charged cations resulted in compounds with an increased somatostatin receptor affinity [21]. Froidevaux *et al.* reported that DOTATOC is clearly superior to DTPAOC as indicated by its uniquely high tumor-to-non-target tissue ratio [7].

Our data showed that the uptakes of both In-111 DTPAOC and In-111 DOTATOC in the kidneys were as high as those in the tumors. The high uptake of In-111 DTPAOC and In-111 DOTATOC in the kidneys might not be a major problem for diagnostic use since In-111 causes only minor damage to the tissue in the diagnostic low dose. However, if DOTATOC is labeled with a beta emitter such as Y-90 for therapeutic purposes, the high uptake of DOTATOC in the kidneys can be a major problem, causing long-term irreversible damage to this organ. In a recent human study with Y-90 labeled DOTATOC, Paganelli *et al.*

reported radiation dose to the kidneys as a limiting factor with low risk of myelotoxicity [21]. To solve this problem, intravenous administration of D-lysine has been proven to be able to reduce renal uptake significantly with no effect on blood clearance or tumor uptake [1, 10].

In conclusion, In-111 DOTATOC showed significantly higher tumor affinity than In-111 DTPAOC in the rats bearing pancreatic tumors, although both of these radiopharmaceuticals showed expected high tumor uptake.

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