Comparison of ^{111}In-DOTA-Tyr^3-Octreotide and ^{111}In-DTPA-Octreotide in the Same Patients: Biodistribution, Kinetics, Organ and Tumor Uptake

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Scintigraphy with [^{111}In-diethylenetriamine pentaacetic acid^0-D-Phe^1]-octreotide (DTPAOC) is used to demonstrate neuroendocrine and other somatostatin-receptor-positive tumors. Despite encouraging results, this ^{111}In-labeled compound is not well suited for peptide-receptor-mediated radiotherapy of somatostatin-receptor-positive tumors. Another somatostatin analog, [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid^0, D-Phe^1, Tyr^3]-octreotide (DOTATOC), can be labeled with the β-emitter ^{90}Y in a stable manner. **Methods:** We compared the distribution, kinetics and dosimetry of ^{111}In-DTPAOC and ^{111}In-DOTATOC in eight patients to predict the outcomes of these parameters in patients who will be treated with ^{90}Y-DOTATOC. **Results:** Serum radioactivity levels for the radiopharmaceuticals did not differ significantly 2–24 h after injection ($P > 0.05$). Up to 2 h postinjection they were slightly, but significantly, lower after administration of ^{111}In-DOTATOC ($P < 0.01$ at most time points). The percentage of peptide-bound radioactivity in serum did not differ after administration of either compound. Urinary excretion was significantly lower after administration of ^{111}In-DOTATOC ($P < 0.01$). The visualization of known somatostatin-receptor-positive organs and tumors was clearer after administration of ^{111}In-DOTATOC than after administration of ^{111}In-DTPAOC. This was confirmed by significantly higher calculated uptakes in the pituitary gland and spleen. The uptake in the tumor sites did not differ significantly ($P > 0.05$), although in three of the four patients in whom tumor uptake could be calculated, it was higher after administration of ^{111}In-DOTATOC. **Conclusion:** The distribution and excretion pattern of ^{111}In-DOTATOC resembles that of ^{111}In-DTPAOC, and the uptake in somatostatin-receptor-positive organs and most tumors is higher for ^{111}In-DOTATOC. If ^{90}Y-DOTATOC shows an uptake pattern similar to ^{111}In-DOTATOC, it is a promising radiopharmaceutical for peptide-receptor-mediated radiotherapy in patients with somatostatin-receptor-positive tumors.

Key Words: somatostatin; somatostatin receptor; [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid^0, D-Phe^1, Tyr^3]-octreotide; ^{111}In-diethylenetriamine pentaacetic acid^0-D-Phe^1-octreotide; scintigraphy

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Scintigraphy with the radiolabeled somatostatin analog [^{111}In-diethylenetriamine pentaacetic acid^0-D-Phe^1]-octreotide ([DTPAOC] OctreoScan®; Mallinckrodt, Inc., Petten, The Netherlands) has gained acceptance as a diagnostic procedure for demonstrating neuroendocrine and other somatostatin-receptor-positive tumors. Therapy with high dosages of this ^{111}In-labeled compound may result in tumor regression in some patients with somatostatin-receptor-positive tumors (*1*). A recent update of 16 patients who had progressive tumor growth before the start of the therapy and who were treated with a cumulative dose of at least 20 GBq showed documented tumor regression in five patients, stable disease in five and tumor progression in the other six (*2*). The observed tumor regression in some of the patients may be ascribed to Auger or conversion electrons. However, the development of ^{90}Y-coupled somatostatin analogs may be more promising for therapeutic use because of the much higher energy and longer range of the ^{90}Y-β-particles (2.28 MeV, range 1.1×10^{-2} m) compared with the Auger electrons of ^{111}In (2.6 keV, range 3.7×10^{-7} m). This implies that in tumors with a heterogeneous distribution of somatostatin receptors (e.g., breast tumors) effective radiotherapy may also become possible. Furthermore, internalization in the tumor cells is not required using ^{90}Y-coupled analogs because of the "cross-fire" β-irradiation within a range of 11 mm.

Because ^{90}Y cannot be linked in a sufficiently stable way to DTPA, another somatostatin analog, [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid^0, D-Phe^1, Tyr^3]-octreotide (DOTATOC), was developed. The β-emitter ^{90}Y can be linked to this analog in a stable manner (*3*). Preliminary data on the use of this compound for treatment of somatostatin-receptor-positive tumors were recently published (*4,5*).

In this study, we compared the distribution, kinetics and dosimetry of ^{111}In-DTPAOC and ^{111}In-DOTATOC in the same patients to predict the outcomes of these parameters in patients who will be treated with ^{90}Y-DOTATOC, assuming that the metabolism of ^{90}Y-DOTATOC resembles that of ^{111}In-DOTATOC.

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MATERIALS AND METHODS

Patients

In eight patients (five women, three men; age range 27–66 y) scintigraphy with ^{111}In-DTPAOC and ^{111}In-DOTATOC was performed. The time between both investigations ranged from 3 to 5 wk. Sandostatin (Octreotide; Sandoz, Basel, Switzerland) medication was discontinued 48 h before the injection of the radiopharmaceutical and resumed 24 h later or thereafter.

Three patients had medullary thyroid carcinoma (MTC), one had carcinoid syndrome, one had a gastrinoma, one metastatic (pancreatic) adenocarcinoma, one had liver metastases of an operated pancreatic neuroendocrine tumor and one patient was screened for pheochromocytoma because she had multiple endocrine neoplasia syndrome.

Methods

^{111}In-DTPAOC was prepared using the OctreoScan®-kit from Mallinckrodt, Inc. The mean injected dose was 204 MBq (range 191–212 MBq), coupled to 8–9 μg DTPAOC. The synthesis of DOTATOC will be described elsewhere. Kits were prepared consisting of 10 μg DOTATOC in 7 μL milliQ-water (Waters, Milford, MA), 110 μL 0.2 mol/L ammoniumacetate and 1 mg gentisic acid in 83 μL 0.05 mol/L acetic acid. Kits were stored at −20°C until use. $^{111}InCl_3$ was added, and the mixture was heated for 30 min at 100°C. The labeling yield was checked using instant thin-layer chromatography (ITLC-SG, Gelman, Ann Arbor, MI) and 0.1 mol/L NaCitrate, pH 5.0, and the radiochemical purity was checked by high-performance liquid chromatography (HPLC), as previously described (*6*). Labeling yields of both ^{111}In-DOTATOC and ^{111}In-DTPAOC always exceeded 99%, whereas radiochemical purity (activity bound to DOTATOC and DTPAOC, as measured by HPLC) was always higher than 95%. The mean injected dose was 183 MBq (range 141–202 MBq), coupled to 8–9 μg DOTATOC.

Imaging

Planar imaging was performed with a double-head camera (Picker International, Inc., Cleveland, OH) equipped with a medium-energy collimator. The windows were centered over both ^{111}In photon peaks (172 and 245 keV) with a window width of 20%. Dynamic images of the upper abdomen were obtained from the time of injection up to 20 min postinjection. Static spot images were obtained 4, 24 and 48 h postinjection. Preset time was 15 min.

SPECT images of the regions of interest (ROIs) were obtained 24 h postinjection with a three-head camera (Picker International, Inc.). Acquisition consisted of 120 projections, with an acquisition time of 30 (abdomen) to 45 s (head and thorax) per projection. SPECT analysis was performed with a Wiener filter on original data. The filtered data were reconstructed with a ramp filter. The examination and comparison of the scans were performed conjointly.

Measurement of Radioactivity in Blood, Urine and Feces

Radioactivity in blood, urine and feces was measured with a Ge-detector equipped with a multichannel analyzer (series 40, Canberra, Zellik, Belgium). Blood samples were drawn 10, 20, 40, 60 and 90 min, and 2, 4 and 24 h after injection. Urine was collected in two 3-h intervals and thereafter at 12 and 24 h after injection. In some patients, feces was also collected up to 48 h after injection. The chemical status of the radionuclide in blood and urine was analyzed as a function of time by SEP-PAK C_{18}, HPLC and gel filtration techniques as described previously (*7*).

In Vivo Measurements

The uptakes in the most important somatostatin-receptor-positive tissues and/or organs involved in the metabolism or excretion of the somatostatin analogs were determined, i.e., in the pituitary gland, liver, spleen, kidneys and, when feasible, visualized tumors. Radioactivity in these tissues was calculated as previously described (*8*). Dosimetric calculations were performed using the MIRDOSE package, version 3.0 (RIDIC, Oak Ridge, TN).

Statistics

Analysis of variance (ANOVA) and, when applicable, paired *t* tests were used. $P < 0.05$ was considered significant.

RESULTS

The distribution patterns of ^{111}In-DOTATOC and ^{111}In-DTPAOC were comparable directly after injection, with rapid visualization of the kidneys, and at 4 h postinjection, when relatively high background radioactivity was present, with visualization of the liver, spleen, kidneys and, in some of the patients, the pituitary and thyroid glands and tumors.

In four patients, serum radioactivity after administration of ^{111}In-DOTATOC and ^{111}In-DTPAOC was measured. During the first 2 h, circulating radioactivity expressed as a percentage of the injected dose was slightly, but significantly, higher after ^{111}In-DTPAOC administration; thereafter, serum radioactivity levels did not differ significantly (ANOVA tests, $P > 0.05$) (Fig. 1).

Peptide-bound radioactivity in serum, expressed as a percentage of the total serum radioactivity, did not differ significantly in the four patients after ^{111}In-DOTATOC or ^{111}In-DTPAOC administrations at various time points. Up to 2 h postinjection, percentages of peptide-bound radioactivity were typically 80%–90% for both radiopharmaceuticals (data not given). In the first fractions eluted from the SEP-PAK C_{18} (polar solvents), radioactivity was present as ^{111}In-DTPA or ^{111}In-DOTA or as radiopharmaceutical, bound to the plasma proteins. The possibility of ^{111}In-DTPA-Phe or ^{111}In-DOTA-Phe can be excluded because these amino acids elute from the SEP-PAK with the apolar solvent. After more than 4 h, when plasma radioactivity was already less than 5% of the injected dose, the percentages of peptide-bound radioactivity tended to be lower after administration of ^{111}In-DTPAOC (after 280 min and 24 h mean percentages were 69% and 7% after ^{111}In-DTPAOC, versus 86% and 22% after ^{111}In-DOTATOC, respectively).

Urinary radioactivity in the first 24 h after the injection of ^{111}In-DOTATOC and ^{111}In-DTPAOC was measured in six patients (Fig. 2). Levels were significantly lower after ^{111}In-DOTATOC administration (ANOVA, $P < 0.01$).

Peptide-bound radioactivity in urine collected up to 3, 6, 12 and 24 h postinjection was measured in the same six patients after administration of ^{111}In-DOTATOC and ^{111}In-DTPAOC. At no time interval was a significant difference between the two radiopharmaceuticals observed. Peptide-bound radioactivity was more than 90% up to 6 h postinjection, approximately 90% at 12 h postinjection and approximately 80% at 24 h postinjection (data not given).

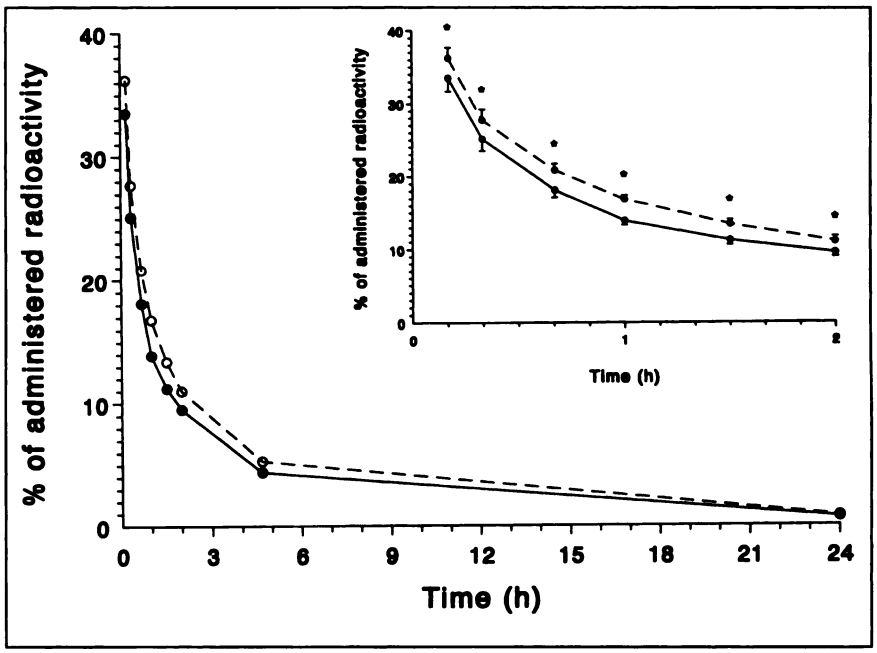

FIGURE 1. Mean (±SEM) serum radioactivity expressed as percentage of injected dose in same four patients. Open circles, dashed line = ^{111}In-DTPAOC; filled circles, solid line = ^{111}In-DOTATOC; asterisks = significantly different from other radiopharmaceutical (ANOVA, paired *t* test).

Radioactivity in feces was measured up to 24 h in three patients and up to 48 h in two of these after injection of ^{111}In-DOTATOC. Levels were less than 1% of the injected dose in all patients after 24 h, and the cumulative quantity was less than 2% of the injected dose in the two patients in whom it was measured up to 48 h postinjection.

On examination of the scans obtained 24 and 48 h postinjection, the visualization of the pituitary gland was clearer in all eight patients after administration of ^{111}In-DOTATOC (Fig. 3); visualization of the spleen was clearer in three of eight patients. The uptake was considered equal in the remaining five patients. The uptake in the liver seemed lower after administration of ^{111}In-DOTATOC than after administration of ^{111}In-DTPAOC in five of eight patients and nearly equal in the remaining three; whereas the visualization of the thyroid gland was less clear in two patients, equal in two, and no thyroid uptake was recognized in the other four. Easily recognizable abnormal accumulation of radioactivity at sites of pathology was evident on planar images in five patients. Marginally visible increased uptake at supposed sites of pathology was seen in two other patients. In these seven patients, increased uptake was clearer after administration of ^{111}In-DOTATOC than after ^{111}In-DTPAOC (Figs. 4 and 5). In the remaining patient, only SPECT imaging pointed to a site of potential pathology, indicated by both radiopharmaceuticals.

The uptake of radioactivity as a percentage of the injected dose in organs and tumors was also calculated. The calculated uptakes in the pituitary gland and spleen were significantly higher after administration of ^{111}In-DOTATOC than after ^{111}In-DTPAOC, whereas the uptake in the kidneys (except for the 4-h uptake) and the tumors did not differ

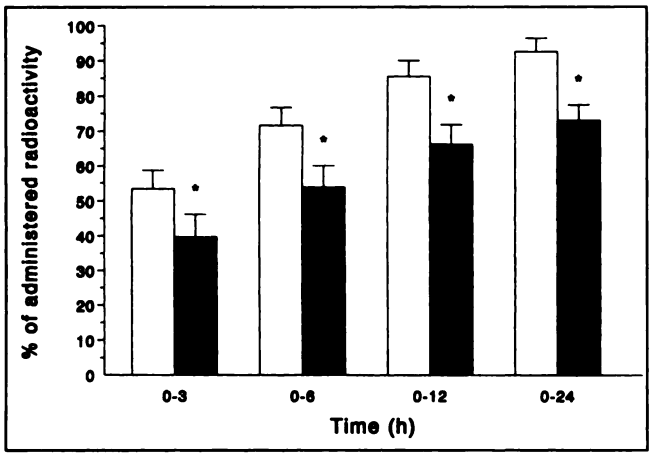

FIGURE 2. Cumulative radioactivity excreted in urine, expressed as mean (± SEM) percentage of injected dose in same six patients. White bars = ^{111}In-DTPAOC; black bars = ^{111}In-DOTATOC; asterisks = significantly different from other radiopharmaceutical (ANOVA, paired *t* test).

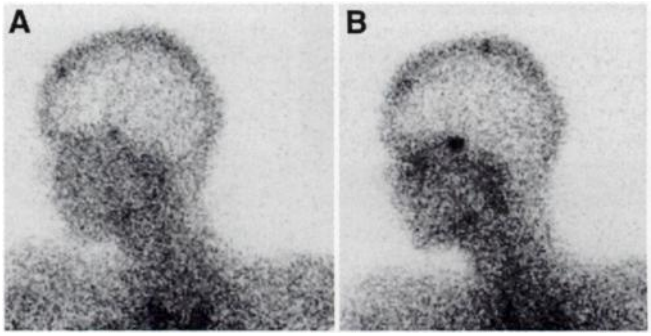

FIGURE 3. Left lateral image of head of patient with MTC, 24 h postinjection. (A) After administration of ^{111}In-DTPAOC. (B) After administration of ^{111}In-DOTATOC. Note better visualization of pituitary gland and also of skull metastases, after ^{111}In-DOTATOC administration.

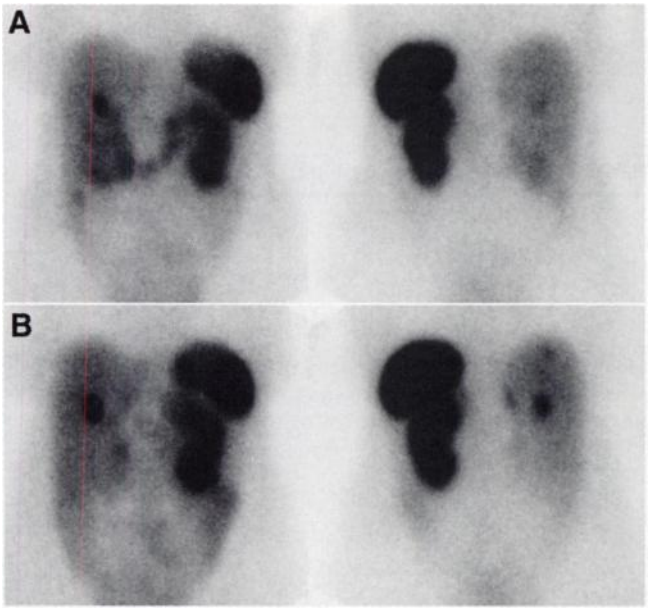

FIGURE 4. Anterior abdominal images in patient with liver metastases of neuroendocrine tumor, 24 h postinjection. (A) After administration of ^{111}In-DTPAOC. (B) After administration of ^{111}In-DOTATOC. Right kidney has been removed. Note better visualization of liver metastases after ^{111}In-DOTATOC administration.

significantly. The uptake in the liver was significantly lower after administration of ^{111}In-DOTATOC than after ^{111}In-DTPAOC (ANOVA tests and paired *t* tests for all calculations [Fig. 6]). In one of the five patients whose tumor uptake was evident on planar imaging, overlapping abdominal uptake with inequal count density influenced the calculations to a great extent, whereas in two others, in whom tumor uptake was low on planar images, the target-to-background ratios were low and too dependent on background ROIs to

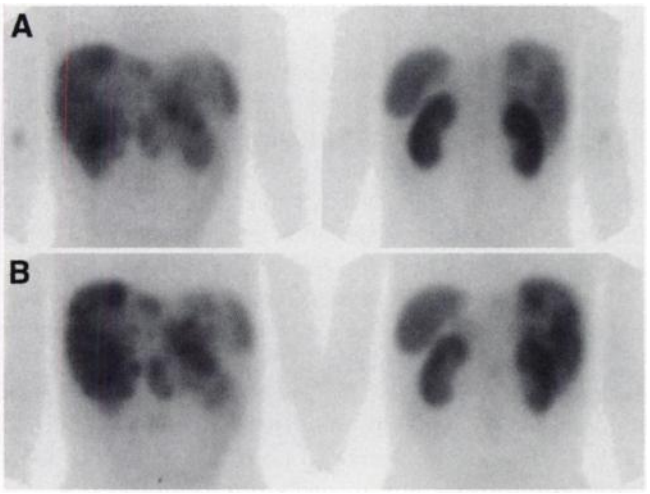

FIGURE 5. Anterior abdominal images in patient with liver metastases of carcinoid tumor, 24 h postinjection. (A) After administration of ^{111}In-DTPAOC. (B) After administration of ^{111}In-DOTATOC. There is cold area in liver due to tumor necrosis. Note better visualization of liver metastases after ^{111}In-DOTATOC administration.

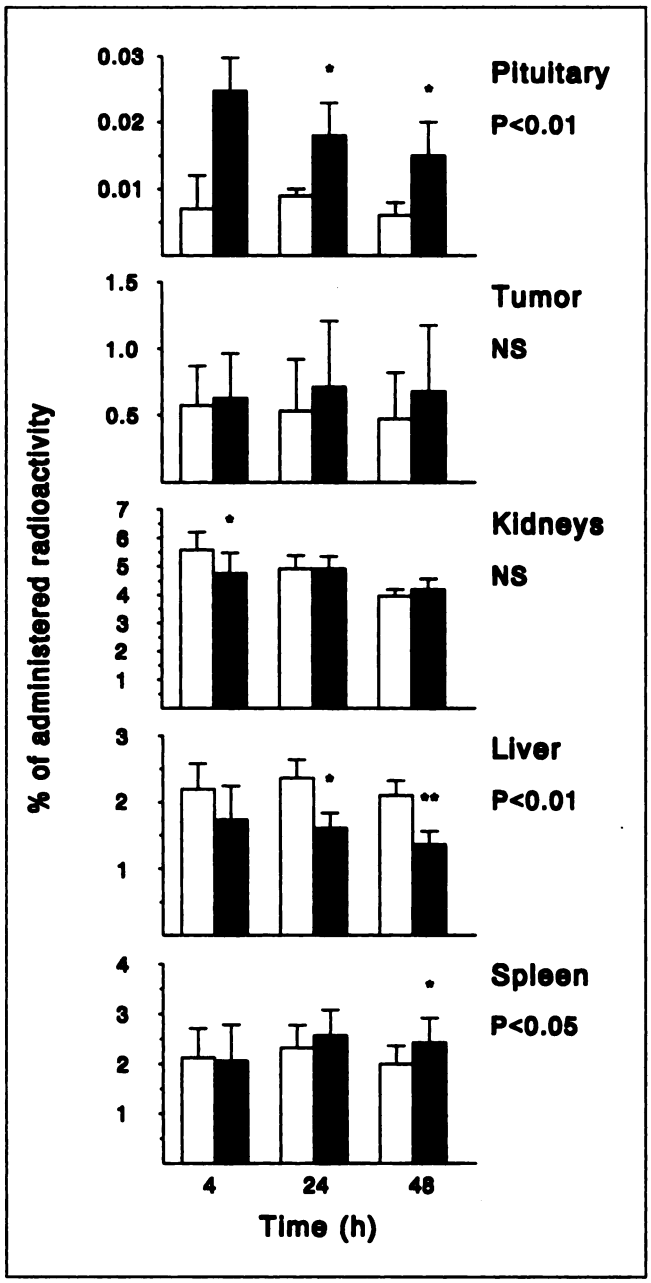

FIGURE 6. Uptake of radioactivity in organs and tumor sites, expressed as mean (±SEM) percentage of administered dose in same eight patients. White bars = ^{111}In-DTPAOC; black bars = ^{111}In-DOTATOC. Statistics on right-hand side refer to ANOVA with radiopharmaceutical, time and patient as independent variables. $^{*}P < 0.05$ and $^{**}P < 0.01$ at individual time points (paired *t* tests). Liver uptake pertains to seven patients, and tumor uptake to four patients.

be reliable. The uptake in tumor sites was computed in four patients; in three of these four patients, calculated uptakes in the tumor were higher after administration of ^{111}In-DOTATOC than after ^{111}In-DTPAOC (Table 1). Compared with the 4-h calculated tumor uptake, the 24- and 48-h uptakes were lower in a patient with MTC (Table 1). This patient's tumor was in the thorax, and overprojection of heart and vessel radioactivity at 4 h, being virtually negli-

TABLE 1
Calculated Uptake in Tumors from Four Patients

Tumor	Uptake (% injected dose)					
	4 h		24 h		48 h	
	^{111}In-DTPAOC	^{111}In-DOTATOC	^{111}In-DTPAOC	^{111}In-DOTATOC	^{111}In-DTPAOC	^{111}In-DOTATOC
Gastrinoma (Abd)	0	0.05	0	0.04	0	0.05
Apudoma (Liver)	—	—	0.15	0.30	0.14	0.24
MTC (Thorax)	0.70	0.60	0.30	0.24	0.23	0.19
Carcinoid (Abd)	1.01	1.23	1.68	2.25	1.52	2.23

DTPAOC = [diethylenetriamine pentaacetic acid^0-D-Phe^1]-octreotide; DOTATOC = [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid^0, D-Phe^1, Tyr^3]-octreotide; Abd = abdomen; — = data not available; MTC = medullary thyroid carcinoma.

gible at 24 h, probably accounts for this finding. In a patient with abdominal carcinoid tumor, the calculated uptake at 24 and 48 h was significantly higher than at 4 h (Table 1). This patient had right-sided heart failure due to carcinoid-syndrome-induced tricuspid insufficiency; the reduced cardiac output and, consequently, the reduced renal clearance of the radiolabeled somatostatin analogs might explain the increase in tumor uptake with time in this patient.

Dosimetric calculations are listed in Table 2. The absorbed doses for the most important target organs and the effective dose were comparable. For comparison, the absorbed doses for ^{90}Y-DOTATOC, assuming a similar distribution as for ^{111}In-DOTATOC, are also listed.

DISCUSSION

This study demonstrates that the distribution and pattern of organ uptake of ^{111}In-DOTATOC are similar to that of ^{111}In-DTPAOC, with some small but important differences. The percentages of peptide-bound serum radioactivity for the two radiopharmaceuticals were identical during the first 2 h after injection, which is the most important time for receptor binding because total circulating radioactivity drops below 10% of the injected dose thereafter.

During these first 2 h, serum levels after administration of ^{111}In-DOTATOC were slightly, but significantly, lower. Urinary excretion in the first 3 h, however, was also significantly lower after administration of ^{111}In-DOTATOC than after ^{111}In-DTPAOC. The sum of the calculated uptakes in kidneys, spleen, liver, tumors and pituitary gland could not account for this difference, the mean at 4 h postinjection was 9.2% of the injected dose after administration of ^{111}In-DOTATOC and 10.8% after ^{111}In-DTPAOC. After 24 h, these differences were even larger (urinary excretion was 73.8% and 92.7%, and calculated uptake in organs was 9.8% and 10.3%, after ^{111}In-DOTATOC and after ^{111}In-DTPAOC, respectively). Serum radioactivity levels at these time points did not differ significantly between the radiopharmaceuticals. This means that the interstitial radioactivity after administration of ^{111}In-DOTATOC is higher, especially at the usual time points of scintigraphy, 24 and 48 h postinjection.

Despite the higher background radioactivity caused by higher levels of interstitial radioactivity, the visualization of known somatostatin-receptor-positive organs and tumors was clearer after administration of ^{111}In-DOTATOC than after ^{111}In-DTPAOC. This was confirmed by significantly higher calculated uptakes in the pituitary gland and spleen. This is also in agreement with a recent study performed on rats, demonstrating significantly higher uptakes in somatostatin-receptor-positive organs after administration of ^{111}In-DOTATOC than after ^{111}In-DTPAOC (*3*). In this study, we found no significant difference between the uptake in the tumor sites, but this may be explained by the small number of tumors (four) on which reliable calculations could be performed. A recent study by Otte et al. (*4*) reported higher tumor-to-kidney ratios for ^{111}In-DOTATOC than for ^{111}In-DTPAOC, based on counts-to-pixel ratios, although no dosimetric calculations were included.

Assuming that the distribution of ^{90}Y-DOTATOC is the same as that of ^{111}In-DOTATOC, organ doses can be calculated. After the administration of 3.7 GBq ^{90}Y-DOTATOC, the dose to kidneys, liver and spleen would be 2240, 100 and 1980 cGy, respectively (Table 2). This means

TABLE 2
Comparison Between Dose Estimates After ^{111}In-DTPAOC and ^{111}In-DOTATOC, Based on Gamma Camera Measurements and Urinary Excretion

Target organ	Absorbed dose (mGy/MBq)		
	^{111}In-DTPAOC	^{111}In-DOTATOC	^{90}Y-DOTATOC
Kidneys	0.47	0.50	6.05
Liver	0.07	0.05	0.27
Spleen	0.36	0.47	5.36
Urinary bladder wall	0.19	0.16	1.59
Effective dose	0.05	0.05	0.35

Dose estimates for ^{90}Y-DOTATOC are based on data for ^{111}In-DOTATOC.

DTPAOC = [diethylenetriamine pentaacetic acid^0-D-Phe^1]-octreotide; DOTATOC = [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid^0, D-Phe^1, Tyr^3]-octreotide.

that in patients who are to be treated with ^{90}Y-DOTATOC, the kidneys will be the dose-limiting organs. However, studies comparing the uptake of ^{90}Y-DOTATOC and ^{111}In-DOTATOC in rats show that kidney uptake after administration of ^{90}Y-DOTATOC is significantly lower than after ^{111}In-DOTATOC, whereas the binding to somatostatin-receptor-positive organs and tumors is higher after ^{90}Y-DOTATOC administration (*3*). A pilot study comparing the uptake of ^{111}In-DOTATOC and ^{86}Y-DOTATOC, as well as the effects of treatment with ^{90}Y-DOTATOC in the same patients, is soon to be initiated and is expected to provide definite figures on the organ doses after ^{90}Y-DOTATOC injection. Also, the intravenous administration of lysine or other amino acids in patients might reduce ^{90}Y-DOTATOC uptake in the kidneys, as was shown for ^{111}In-DTPAOC in rats and humans (*9,10*).

CONCLUSION

The distribution and excretion pattern of ^{111}In-DOTATOC resembles that of ^{111}In-DTPAOC, and the uptake in somatostatin-receptor-positive organs and most tumors is higher for ^{111}In-DOTATOC than for that of ^{111}In-DTPAOC. Assuming it shows an uptake pattern similar to ^{111}In-DOTATOC, ^{90}Y-DOTATOC is a promising radiopharmaceutical for peptide-receptor-mediated radiotherapy in patients with somatostatin-receptor-positive tumors.

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