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[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate: comparison with [^{111}In-DTPA^{0}]octreotide in patients

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Abstract. The somatostatin analogue [DOTA^{0},Tyr^{3}]octreotate has a nine-fold higher affinity for the somatostatin receptor subtype 2 as compared with [DOTA^{0}, Tyr^{3}]octreotide. Also, labelled with the beta- and gamma-emitting radionuclide lutetium-177, this compound has been shown to have a very favourable impact on tumour regression and animal survival in a rat model. Because of these reported advantages over the analogues currently used for somatostatin receptor-mediated radiotherapy, we decided to compare [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) with [^{111}In-DTPA^{0}]octreotide (^{111}In-octreotide) in six patients with somatostatin receptor-positive tumours. Plasma radioactivity after ^{177}Lu-octreotate expressed as a percentage of the injected dose was comparable with that after ^{111}In-octreotide. Urinary excretion of radioactivity was significantly lower than after ^{111}In-octreotide, averaging 64% after 24 h. The uptake after 24 h, expressed as a percentage of the injected dose of ^{177}Lu-octreotate, was comparable to that after ^{111}In-octreotide for kidneys, spleen and liver, but was three- to fourfold higher for four of five tumours. The spleen and kidneys received the highest absorbed doses. The doses to the kidneys were reduced by a mean of 47% after co-infusion of amino acids. It is concluded that in comparison with the radionuclide-coupled somatostatin analogues that are currently available for somatostatin receptor-mediated radiotherapy, ^{177}Lu-octreotate potentially represents an important improvement. Higher absorbed doses can be achieved to most tumours, with about equal doses to potentially dose-limiting organs; furthermore, the lower tissue penetration range of ^{177}Lu as compared with ^{90}Y may be especially important for small tumours.

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Introduction

Somatostatin receptor imaging with [^{111}In-DTPA^{0}]octreotide (Octreoscan) is nowadays recognised to be an important, if not the primary imaging technique for the localisation and staging of neuroendocrine tumours.

In patients with progressive, metastasised neuroendocrine tumours, radionuclide therapy with high doses of [^{111}In-DTPA^{0}]octreotide is performed with encouraging results [1, 2, 3, 4]. However, ^{111}In-coupled peptides are not ideal for peptide receptor radiotherapy (PRRT) because of the small particle range and the resultant short tissue penetration. Therefore, another radiolabelled somatostatin analogue, [^{90}Y-DOTA^{0},Tyr^{3}]octreotide, was developed. A preliminary study by Otte et al. [5] showed favourable results of [^{90}Y-DOTA^{0},Tyr^{3}]octreotide treatment in five patients with neuroendocrine tumours. Also, a recent analysis of the results of this treatment in a multicentre trial in 22 end-stage patients with progressive disease showed a partial tumour response in two, a minor response in three and stable disease in ten [6]. Paganelli et al. [7] have also reported favourable preliminary results regarding tumour growth with this ^{90}Y-labelled compound.

Recently, it was reported that compared with [DTPA^{0}, Tyr^{3}]octreotide, [DTPA^{0},Tyr^{3}]octreotate (in which the C-terminal threoninol is replaced with threonine) showed improved binding to somatostatin receptor-positive tissues in animal experiments [8]. Also, its DOTA-coupled counterpart, [DOTA^{0},Tyr^{3}]octreotate, labelled with the

beta- and gamma-emitting radionuclide lutetium-177, was reported to have a very successful impact on tumour regression and animal survival in a rat model [9]. Reubi et al. [10] reported a ninefold increase in affinity for the somatostatin receptor subtype 2 for [DOTA^0,Tyr^3]octreotate as compared with [DOTA^0,Tyr^3]octreotide, and a six- to sevenfold increase in affinity for their yttrium-loaded counterparts.

Because of these reported advantages over both somatostatin analogues currently used for PRRT, we decided to study [DOTA^0,Tyr^3]octreotate in patients with somatostatin receptor-positive tumours. It was complexed with ^{177}Lu because this radionuclide, apart from intermediate beta energy, also emits gammas suitable for scintigraphy and subsequent dosimetry.

Materials and methods

Patients

[^{177}Lu-DOTA^0,Tyr^3]octreotate (^{177}Lu-octreotate) was administered in six patients (four women and two men, aged 15–76 years). In five of them, somatostatin receptor imaging with [^{111}In-DTPA^0]octreotide (^{111}In-octreotide), performed during the 3 months preceding ^{177}Lu-octreotate scintigraphy, was available. None of the patients used somatostatin analogues.

One patient had medullary thyroid carcinoma (MTC), one had non-Hodgkin lymphoma (NHL), one had a gastroenteropancreatic (GEP) tumour, one had aesthesioneuroblastoma, one had a remnant of a Hürthle cell carcinoma of the thyroid, and one had papillary thyroid carcinoma.

All patients gave written informed consent to participation in the study, which was approved by the medical ethical committee of the hospital.

Methods

[DOTA^0,Tyr^3]Octreotate was obtained from Mallinckrodt (St Louis, Mo., USA). Kits were prepared consisting of 120 µg [DOTA^0,Tyr^3]octreotate, 37.8 mg sodium ascorbate and 7.5 mg gentisic acid in 300 µl 0.05 *M* HCl. Kits were stored at –20°C until use. $^{177}LuCl_3$ was obtained from Missouri University Research Reactor (MURR; University of Missouri, Mo., USA). $^{177}LuCl_3$ was diluted in 0.05 *M* HCl to a concentration of 11.1 GBq/ml, and 2,220 MBq $^{177}LuCl_3$ was added to each kit. The mixture was heated for 30 min at 80°C. The labeling yield was checked using instant thin-layer chromatography (ITLC-SG, Gelman, Ann Arbor, Mich., USA) with 0.1 *M* Na citrate, pH 5.0, as solvent. The labelled peptide migrated from the origin till Rf=0.67, while the free radionuclide migrated with the solvent front (Rf=1).

The radiochemical purity was determined by high-performance liquid chromatography (HPLC) according to the following procedure. Column: Symmetry C_{18} 4.6×250 mm, 5 µm (Waters, Milford, Mass., USA). Flow: 1 ml/min. Solvent A: methanol; solvent B: 0.06 *M* sodium acetate pH 5.5. From *t*=0 to 6.5 min 100% B; from *t*=6.5 to 7.0 min from 100% B to 50% B; from *t*=7.0 to 27 min from 50% B to 40% B; from *t*=27 min to 27.2 min from 40% B to 100% A; from *t*=27.2 min to 32 min: 100% A.

The labeling yield always exceeded 98% and the radiochemical purity was higher than 88%. The injected dose was 1,850 MBq (range 1,847–1,874 MBq); the injected mass of [DOTA^0,Tyr^3]octreotate was 90–100 µg.

^{111}In-octreotide was prepared using the Octreoscan kit from Mallinckrodt Medical (Petten, the Netherlands). The injected dose was about 220 MBq, coupled to 8–9 µg [DTPA^0]octreotide.

Imaging

^{177}Lu-octreotate. The infusion volume was 80 ml and the infusion speed was 10 min. The infusion line by which the radiopharmaceutical was administered was thereafter rinsed with about 100 ml saline. Dynamic images of the upper abdomen were obtained from the time of injection up to 20 min p.i. Planar spot images of the upper abdomen and chest in five patients, and of the upper abdomen and the head and neck in the sixth patient, were obtained with a dual-head camera (Picker Prism 2000) 4 h and 1, 3, 10 and 17 days p.i. Counts from both gamma peaks (208 and 113 keV) were collected in separate windows (width 20%). The acquisition time was 15 min/view. For dosimetry, a standard with a known aliquot of the injected dose was also counted.

^{111}In-octreotide. The windows were centered over both ^{111}In photon peaks (245 and 172 keV) with a window width of 20%. Fifteen-minute spot images were obtained 24 h p.i.

Co-infusion of amino acids

In five patients the administration of the same amount and dose of ^{177}Lu-octreotate was repeated 6–9 weeks later. An infusion of amino acids (lysine 2.5%, arginine 2.5% in 1 l 0.9% NaCl; 250 ml/h) was started 30 min before the administration of the radiopharmaceutical and lasted up to 3.5 h afterwards. Via a second pump system the radiopharmaceutical was co-administered.

Measurement of radioactivity in blood and urine

Blood samples were drawn 10, 20, 40, 60 and 90 min and 2, 5 and 24 h after injection. Urine was collected at two 3-h intervals and thereafter up to 24 h after injection.

Radioactivity in blood and urine was measured with a COBRA-Packard auto-gamma counting system (Packard, Meriden, Conn., USA).

The chemical status of the radionuclide in blood and urine was analysed as a function of time by HPLC techniques (see above).

In vivo measurements

The uptake in organs and tumours was calculated as described previously [11]. Dosimetric calculations were performed using the MIRDOSE package, version 3.0.

Statistics

Analysis of variance (ANOVA) and paired *t* tests were used. *P* values <0.05 were considered significant.

Results

No side-effects or changes in ECG pattern or pulse rate were observed in any patient during the 10-min infusion

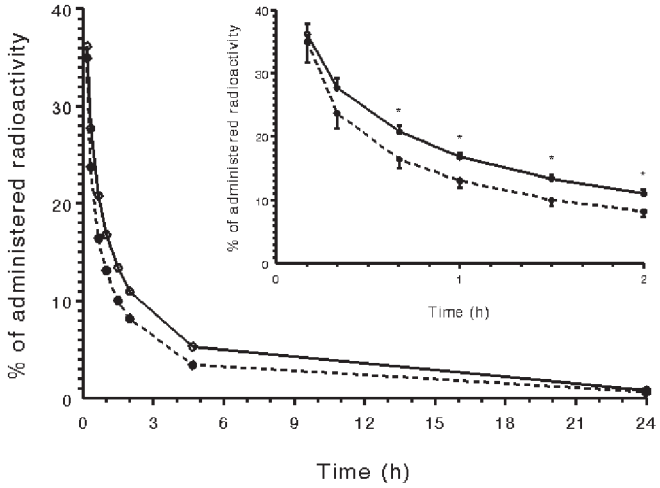

Fig. 1. Mean (±SEM) plasma radioactivity expressed as percentage of the injected dose in six patients after ^{177}Lu-octreotate (*closed dots, stippled line*), compared with that in four other patients after ^{111}In-octreotide from a previous study [12] (*open dots, solid line*). *P<0.05 vs other radiopharmaceutical at the same time point

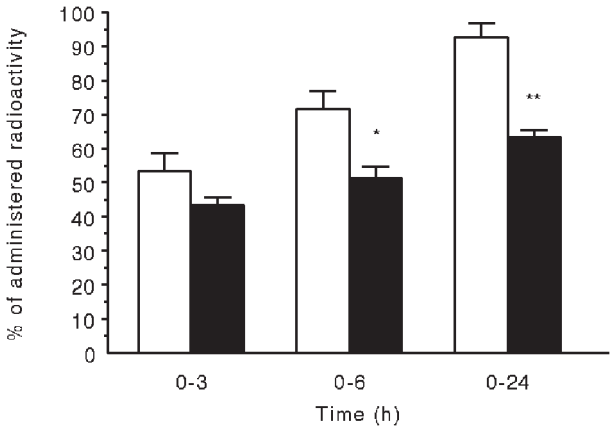

Fig. 2. Cumulative radioactivity excreted in the urine, expressed as mean (±SEM) percentage of the injected dose in four patients after ^{177}Lu-octreotate (*closed bars*), compared with that in six other patients after ^{111}In-octreotide from a previous study [12] (*open bars*). *P<0.05 and **P<0.01 vs other radiopharmaceutical during the same interval

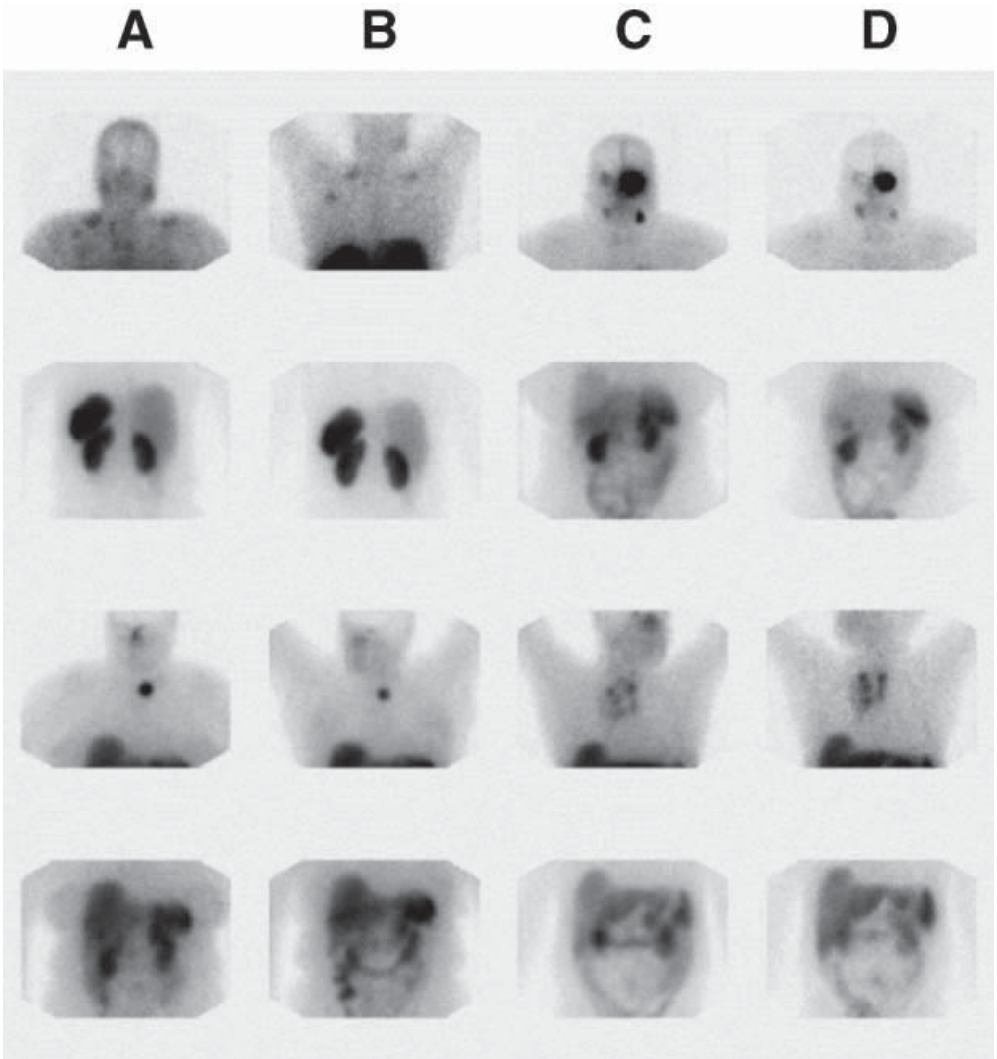

Fig. 3. Images comparing ^{177}Lu-octreotate and ^{111}In-octreotide, 24 h p.i. *Columns A and C:* ^{177}Lu-octreotate; *columns B and D:* ^{111}In-octreotide. The *first row* shows corresponding images of tumour sites in a lymphoma patient (left two images) and a patient with an aesthesioneuroblastoma of the eye with a neck metastasis (right two images); *second row:* posterior (left two images) and anterior abdominal images in the same patients. The *third row* shows corresponding images of tumours in a patient with residual Hürthle cell carcinoma (left two images) and a patient with papillary thyroid carcinoma (right two images); *fourth row:* anterior abdominal images in the same patients. Note the similar biodistribution and the clearer visualisation of the tumour sites, except in the patient with papillary thyroid carcinoma

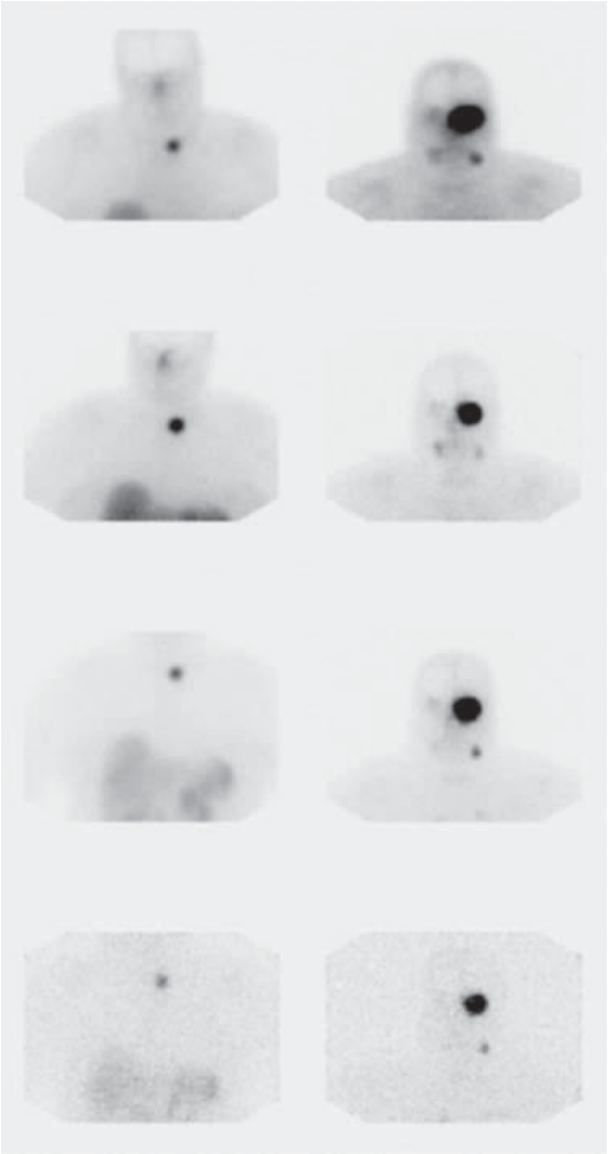

Fig. 4. Images after 4 h and 1, 3 and 17 days (*top row to lower row*) in patients with Hürthle cell carcinoma (*left column*) and aesthesioneuroblastoma (*right column*). Note the retention of radioactivity in the tumour sites

of ^{177}Lu-octreotate or up to 20 min thereafter. The distribution pattern of ^{177}Lu-octreotate was comparable to that of ^{111}In-octreotide, with rapid visualisation of the kidneys directly after injection, and with visualisation of the liver, spleen, kidneys and, in some patients, the pituitary, thyroid and tumours 4 h p.i.

Plasma radioactivity after ^{177}Lu-octreotate expressed as a percentage of the injected dose was slightly, but significantly lower compared with ^{111}In-octreotide measurements from a previous study [12]. After 24 h, however, they were comparable (Fig. 1).

HPLC analysis of plasma, taken at 1 h p.i. in two patients, demonstrated the same pattern as the original injection fluid (data not shown).

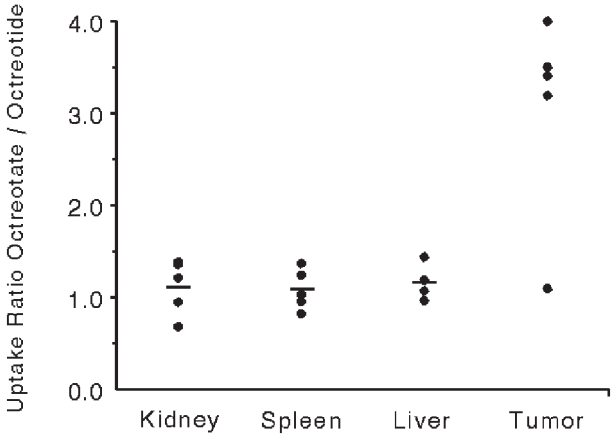

Fig. 5. Ratios of ^{177}Lu-octreotate to ^{111}In-octreotide uptake in organs and tumour sites, with uptake expressed as a percentage of the administered dose. Means are indicated. There is comparable organ uptake and higher tumour uptake after ^{177}Lu-octreotate in most tumours

Table 1. Patient organ doses in cGy (rad)/3,700 MBq (100 mCi)

Patient	Kidneys		Liver	Spleen	Bone marrow
	Without AA	With AA			
1	825	403	90	803	26
2	533	–	76	1,010	29
3	692	282	112	770	27
4	359	252	44	662	27
5	648	366	75	740	20
Mean	611	326	79	797	26

With AA: Kidney dose after amino acid co-infusion

Urinary excretion of radioactivity in the first 24 h after the injection of ^{177}Lu-octreotate is shown in Fig. 2. In comparison with ^{111}In-octreotide, the urinary excretion was significantly lower after ^{177}Lu-octreotate, averaging 64% after 24 h. Peptide-bound radioactivity in urine collected after 1 h in one patient showed the same pattern as the original injection fluid (data not shown).

The scans obtained 24 h p.i. showed the same biodistribution for ^{177}Lu-octreotate and ^{111}In-octreotide, with comparable uptake in the liver, spleen and kidneys (Fig. 3). Also, variable radioactivity was seen in the bowel and urinary bladder. The uptake in the tumours seemed higher after ^{177}Lu-octreotate, except in the patient who had papillary thyroid carcinoma (Fig. 3). At later time points, there was retention of the radioactivity in the tumours, even 17 days p.i. (Fig. 4). The calculated, background-corrected, uptake 24 h after ^{177}Lu-octreotate expressed as a percentage of the injected dose was comparable to that after ^{111}In-octreotide for kidneys, spleen and liver, but was three- to fourfold higher for four of the five tumours (Fig. 5). In the patient with papillary thyroid carcinoma, this uptake was about the same after both radiopharmaceuticals.

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