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ORIGINAL ARTICLE

Biokinetics and dosimetry of ^{111}In-DOTA-NOC-ATE compared with ^{111}In-DTPA-octreotide

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Abstract
Purpose The biokinetics and dosimetry of ^{111}In-DOTA-NOC-ATE (NOCATE), a high-affinity ligand of SSTR-2 and SSTR-5, and ^{111}In-DTPA-octreotide (Octreoscan™, OCTREO) were compared in the same patients.
Methods Seventeen patients (10 men, 7 women; mean age 60 years), referred for an OCTREO scan for imaging of a neuroendocrine tumour (15), thymoma (1) or medullary thyroid carcinoma (1), agreed to undergo a second study with NOCATE. Whole-body anterior–posterior scans were recorded 0.5 (100 % reference scan), 4, 24 and 48 h (17 patients) and 120 h (5 patients) after injection. In 16 patients the OCTREO scan (178±15 MBq) was performed 16±5 days before the NOCATE scan (108±14 MBq) with identical timing; 1 patient had the NOCATE scan before the OCTREO scan. Blood samples were obtained from 14 patients 5 min to 48 h after injection. Activities expressed as percent of the initial (reference) activity in the whole body, lung, kidney, liver, spleen and blood were fitted to biexponential or single exponential functions. Dosimetry was performed using OLINDA/EXM.
Results Initial whole-body, lung and kidney activities were similar, but retention of NOCATE was higher than that of OCTREO. Liver and spleen uptakes of NOCATE were higher from the start ($p<0.001$) and remained so over time. Whole-body activity showed similar α and β half-lives, but the β fraction of NOCATE was double that of OCTREO. Blood $T_{1/2}\beta$ for NOCATE was longer (19 vs. 6 h). As a result, the effective dose of NOCATE (105 μSv/MBq) exceeded that of OCTREO (52 μSv/MBq), and the latter result was similar to the ICRP 106 value of 54 μSv/MBq. Differential activity measurement in blood cells and plasma showed an average of <5 % of NOCATE and OCTREO attached to globular blood components.
Conclusion NOCATE showed a slower clearance from normal tissues and its effective dose was roughly double that of OCTREO.

Keywords ^{111}In-DOTA-NOC-ATE · ^{111}In-DTPA-octreotide · Biokinetics · Dosimetry · Neuroendocrine tumours · Somatostatin receptor

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Introduction

The somatostatin receptor (SSTR), identified by Reubi et al. [1], can be expressed as five different subtype forms (SSTR 1 to 5) [2]. ^{111}In-labelled DTPA-octreotide (Octreoscan™; referred to here as OCTREO) binds with high and moderate affinity to SSTR 2 and 5 (IC_{50} 2 and 22 nmol/l, respectively), and with low affinity to SSTR 3 (IC_{50} 187 nmol/l) [3]. SSTR 2 is expressed in most neuroendocrine tumours, but

may occasionally be absent while other SSTR subtypes can be present [4]. New analogues of somatostatin including DOTA-NOC-ATE have been described [5]. ^{111}In-DOTA-NOC-ATE binds with high affinity to SSTR subtypes 2 and 5 (IC_{50} 2 and 4.3 nmol/l, respectively), with moderate affinity to SSTR 3 (IC_{50} 13 nmol/l) and with low affinity to SSTR 4 (IC_{50} 160 nmol/l) [3] (Fig. 1). In the present study, the biodistribution and dosimetry of NOCATE were prospectively studied in comparison with those of OCTREO.

DOTA-conjugated reagents have the advantage of strongly chelating radiometals. Such reagents include the γ and positron emitters ^{111}In and ^{68}Ga and therapeutic β^- radiation emitters of high energy (^{90}Y) and intermediate energy (^{177}Lu). In this prospective comparative study, we decided to use ^{111}In-labelled NOCATE and OCTREO to take advantage of the identical scintigraphic qualities of the two reagents.

The relevance for scintigraphy and for therapy of the affinity towards particular SSTRs is not known. However, It is reasonable to assume that the log difference in affinity for receptor subtypes of NOCATE compared with OCTREO could play a role in its uptake in tumour and normal tissues that express these subtypes.

The aim of this study was therefore to evaluate whether the higher affinity of NOCATE for SSTRs 3 and 5 compared with OCTREO influences the biodistribution and biokinetics in patients with neuroendocrine tumours. With this perspective, we compared the two ^{111}In-labelled radiopharmaceuticals in patients referred for diagnostic imaging with OCTREO. In a subgroup of 14 patients, blood samples were taken at the time of imaging. Here we present the first head-to-head comparison of the biokinetics and dosimetry of NOCATE with OCTREO. Evaluation of tumour imaging with the two reagents will be reported separately.

Patients and methods

This prospective, comparative study was authorized by the local Ethics Committees of the Lausanne and Geneva University Hospitals, by Swissmedic and the Swiss Federal Office of Public Health (OFSP), Section of Radioprotection, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients gave their written informed consent to participate in the study.

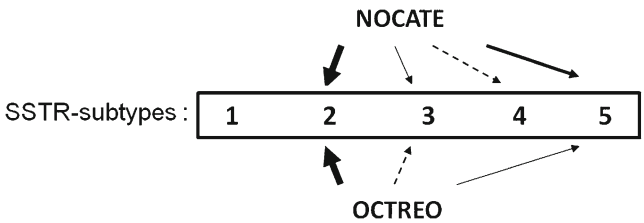

Fig. 1 Affinity profiles of OCTREO and NOCATE as reported previously [5]. Affinities from high to low (IC_{50} values from low to high): *thick arrows*, *medium arrow*, *thin arrows*, *broken arrows* (IC_{50}> 100 nmol/L). The IC_{50} values of OCTREO for SSTRs 2, 5 and 3 are 2±0.7, 22±6 and 187±55 nmol/L (mean ± SE), respectively. The IC_{50} values of ^{111}In-NOCATE for SSTRs 2, 5, 3 and 4 are 2±0.6, 4.3±0.5, 13±4 and 160±3.8 nmol/L (mean ± SE), respectively [5]

Patients with a diagnosis of a tumour expected to express SSTR who were referred for an OCTREO scan were invited to participate in the study provided they were aged ≥18 years, capable of providing informed consent and had a Karnofsky index of ≥60 %. Exclusion criteria were the presence of any severe infection, bone marrow insufficiency with leucocytes <2,500/μl or platelets <100,000/μl, liver or kidney disease with transaminases (AST/ALT), bilirubin or creatinine more than twice the upper limits of normal, and participation in another study. Pregnant and breastfeeding women were excluded, and all participants had to agree to 3 months of contraception after the first clinical study with NOCATE. Of the 17 patients, 15 had a neuroendocrine tumour, and 1 each had a thymoma and a medullary thyroid carcinoma. Four patients had no detectable tumour at the time of the study.

OCTREO

Labelling and administration of OCTREO (10 μg, 178± 15 MBq per patient; the formulation containing trisodium citrate, citric acid and inositol as well gentisic acid) and scintigraphy were performed according to the manufacturer's (Mallinckrodt, Maryland Heights, MO) instructions. Planar whole-body (WB) scintigraphy was performed at 0.5 h without bladder voiding (100 % reference scan) and at 4, 24 and 48 h (empty bladder) after injection. Five patients agreed to have an additional scan at 120 h after injection of OCTREO and after injection of NOCATE. Scanning was performed on a dual-head gamma camera (Biad; Trionix Research Laboratory, Twinsburg, OH) in a 256×1,024 matrix, using a medium energy collimator and narrow energy windows of 171±15 % and 245±15 %keV with the detector heads at a stable distance. A standard containing 1.8 MBq ^{111}In in 10 ml prepared at the time of the first scan was scanned at each time point and in the identical position immediately before the patient was scanned.

NOCATE

The NOCATE precursor was prepared in a documented, controlled manner. The final analysis, including controls of organic and inorganic solvents and an acute toxicity study, were evaluated at independent institutions. Toxicity at a dose of 1.5 mg/kg (5,000-fold patient dose) was tested in six female HanLbm NMRI mice (SPF) according to OECD Guidelines for the Testing of Chemicals no. 432 and

Directive 96/54/EEC, B.1 trials. The animal study (RCC study no. 849627) was performed in an AAALAC-approved laboratory in accordance with Swiss Animal Protection laws under license no. 82 at RRC Ltd., Füllinsdorf, Switzerland. NOCATE at the controlled level was shown to be not toxic.

NOCATE (20 μg in 50 μl aqueous solution) was radiolabelled with 111 MBq ^{111}In in 0.3-ml aqueous solution. ^{111}In was buffered with 40 μl sodium acetate 0.3 M (pH 4.5 to 5), mixed with the peptide and incubated for 0.5 h at 100 °C. The labelling solution was buffered with 0.11 ml 0.573 M Na_2HPO_4 and 5 ml physiological NaCl solution was added. After filtration through a Millipore 0.2-μm sterile filter, the final patient solution was ready for use, provided the radiochemical purity of ≥95 % had been reached. Under these conditions with kit formulations and peptide in solution (20 μg), the desired injection activity of NOCATE was obtained at a radiochemical purity of >95 % in all patients.

NOCATE was administered after a planned delay of 2 weeks from the OCTREO scan, except in one patient who had the NOCATE scan first followed with the same delay by the OCTREO scan. No particular difference in biodistribution compared with the other patients was observed in this latter patient whose data were therefore handled in the same manner as those of all other patients. After intravenous injection of 108±14 MBq ^{111}In-NOCATE, scintigraphy was performed at 0.5, 4, 24 and 48 h and in five patients also at 120 h after injection. Again, a standard sample of 1.8 MBq ^{111}In (prepared at the time of the initial NOCATE scan) was scanned immediately before the patients. In all individual patients, the number and time-points of the NOCATE and OCTREO scans and for the blood sampling were identical.

Biodistribution

Regions of interest were drawn contouring the whole body and organs on the anterior and posterior views. After background correction and calculating the geometric mean, activity was expressed as percent of total body activity of the scan obtained 30 min after injection representing the injected activity. Regarding the lungs, contouring was performed so as to minimize mediastinal scatter. Kidney background correction was performed by defining the activity in an external circular crescent from the upper to lower poles of the kidney and correcting the activity of the renal surface with respect to that of the crescent. We estimated that the underlying liver activity on the right kidney was adequately subtracted in this way. In most patients liver metastases were not observed and when they were occasionally seen, the background correction would, in our opinion, have adequately dealt with them. Corrected kidney uptake was measured on posterior images only and expressed as percent of the posterior WB scan. Attenuation and scatter correction were not performed in this study.

Activities at different scan times were corrected for the physical half-life of ^{111}In. WB, lung, liver, spleen, kidney and bladder activities as well as activities in the remainder of the body are expressed as percent of injected activity (initial WB scan) in all patients. The activity of the standard sample (prepared at the time of the first scan) was measured, and corrected for background and decay to evaluate the stability of the scanner and procedure.

Blood sampling

Blood samples were taken at 5, 15, 30 and 60 min and at 4, 24 and 48 h after injection in 14 patients (9 men, 5 women). In 5 patients blood samples were also taken at 120 h. The activity of 1-ml aliquots from all collected blood samples was counted on the last study day, 48 or 120 h after injection. In seven patients activity was analysed separately for the globular fraction and plasma and the haematocrit value of each patient was used to determine the respective volumes.

Half-lives of organs, total body, remainder of body and blood activities

WB, lung, liver and blood activities were fitted to biexponential functions for male and female patients and then also for all patients together using UNISTAT 5.6 statistical package for Windows (Unistat, London). The results of the biexponential function fittings are given as means ± standard error. Kidney and spleen activities fitted best to single exponential functions that were performed on Excel in all patients individually. Results of the single exponential functions are given as means ± 1 SD.

Dosimetry

OLINDA (OLINDA/EXM 1.0; Vanderbilt University) was used to calculate organ and tissue radiation doses from OCTREO and NOCATE [6]. According to the published method, red marrow residence time was extrapolated from the blood residence time assuming identical extracellular activity concentrations and half-lives and setting the blood to marrow residence time ratio to 0.091 [7]. The urinary bladder model [6] was used to evaluate the residence time for bladder. We assumed for OCTREO (in accordance with ICRP guidelines) and NOCATE that all activity was

eliminated via the kidneys in the urine. Accordingly the parameter for the kidney elimination fraction was set to 1. The fractions (f) of the biological α and β WB half-lives in patients were introduced into the bladder model and both residence times were summed. The bladder voiding interval used was 2 h. The summed residence times for the bladder of OCTREO and NOCATE were introduced into the OLIDA dose calculations.

Statistical evaluation

Uptake in tissues was compared between NOCATE and OCTREO using the paired Student's t test. Values of $p<0.05$ were considered significant and <0.001 as highly significant. The uncertainty of the residence time, $d\tau$, was determined using the propagation of the uncertainties on f_1, $T_{1/2,1}$, f_2 and $T_{1/2,2}$ (f_1 and f_2 are the prefactors for $T_{1/2}\alpha$ and $T_{1/2}\beta$, respectively) obtained from the least-squares fitting of the biexponential function, as follows [8]:

$$d\tau = 1.44 \cdot \sqrt{\left(\left(\frac{df_1}{f_1}\right)^2 + \left(\frac{dT_{1/2,1}}{T_{1/2,1}}\right)^2\right) \cdot \left(f_1 \cdot T_{1/2,1}\right)^2 + \left(\left(\frac{df_2}{f_2}\right)^2 + \left(\frac{dT_{1/2,2}}{T_{1/2,2}}\right)^2\right) \cdot \left(f_2 \cdot T_{1/2,2}\right)^2}$$

Results

The patient characteristics are presented in Table 1. Injections of OCTREO and NOCATE were well tolerated by all patients.

Biodistribution of NOCATE and OCTREO

For the ^{111}In standards, the differences between the counts of the highest and lowest samples were <2 % in 117 scans (86 %), ≤5 % in 13 scans (10 %) and 5–10 % in and 3 scans (2 %). In the whole body the percent activity of NOCATE was roughly twice that of OCTREO at 24, 48 and 120 h after injection (Table 2). In the lungs and kidneys, the initial uptakes were similar between the two compounds, but NOCATE showed a longer retention than OCTREO ($p<0.05$ and <0.001; Table 2). In the liver and spleen, however, the uptake of NOCATE was higher than that of OCTREO from the start, the half-lives being rather similar (Table 2). In four patients with a major metastatic load (Table 2). the liver was not included in dosimetry. In men and women, although their body weight differed markedly, tissue uptakes, as shown in Table 2, overlapped with no major trend for a difference between genders. All data are therefore presented for the 17 patients combined. Images obtained in an example patient comparing the biodistribution of NOCATE and OCTREO 4 h after injection are shown in Fig. 2.

Table 1 Patient characteristics

Characteristic	Value
Patients (N)	
Women	7
Men	10
Age (years)	
Median	61
Range	44–79
Weight (kg, mean ± SD)	
Women	56±6
Men	82±11
Tumour diagnosis	
Neuroendocrine tumour	15
Thymoma	1
Medullary thyroid carcinoma	1
OCTREO injected	
Activity (MBq, mean ± SD, N=17)	178±15
Amount (μg/patient)	10
NOCATE injected	
Activity (MBq, mean ± SD, N=17)	108±14
Amount (μg/patient)	20
Time between scans (days)	
OCTREO to NOCATE (mean ± SD, N=16)	16±5
NOCATE to OCTREO (N=1)	14

Residence times in organs, total body and blood

For dosimetry, the total body, liver, lungs and blood data were fitted to biexponential functions (Figs. 3, 4 and 5, respectively). The patients were initially divided for analysis according to gender (ten men, seven women), but since the results in these two subgroups were very similar for both OCTREO and NOCATE (OCTREO in accordance with ICRP [9]), the final analysis was performed for all patients together. The measured uptakes in the spleen and kidneys fitted best to single exponential functions that were calculated for each patient individually. For these two organs, the curves (Fig. 4) showed the mean of all half-lives calculated individually. For both genders, the extrapolated residence times of NOCATE were roughly double those of OCTREO, and thus are also given for all patients together (Table 3).

Blood activity of OCTREO (Fig. 5a) showed a high variability over the initial 24 h after injection with very low values

Table 2 WB and organ activities of OCTREO and NOCATE shown as percent of the initial WB activity (scans at 0.5 h, 100 %) in all patients (N=17) unless otherwise stated, corrected for the physical half-life of ^{111}In. Values are means ± SD

Organ	Time (h)									
	0.5		4		24		48 (N=13)		120 (N=5)	
	OCTREO	NOCATE	OCTREO	NOCATE	OCTREO	NOCATE	OCTREO	NOCATE	OCTREO	NOCATE
Whole body	100	100	54.8±13.5	80.4±5.4**	26.5±12.6	59.1±6.7**	20.6±10.1	47.7±6.2**	14.4±7.7	33.4±3.1*
Lungs	3.9±1.1	3.8±0.7	2.4±1.1	2.9±0.5*	0.8±0.4	2.0±0.5**	0.6±0.3	1.5±0.4**	0.5±0.2	1.1±0.2**
Kidneys	3.9±1.3	4.0±1.1	3.6±1.0	3.6±1.0	2.8±0.8	3.6±1.0*	2.0±0.7	3.1±1.1**	1.2±0.3	2.2±0.6**
Liver[a]										
Metastases not observed (N=13)	5.2±1.1	11.8±2.5**	4.0±1.4	10.0±2.4**	2.8±1.0	7.3±2.3**	2.5±1.1	6.3±2.6**	2.4±0.9	5.0±1.4*
Heavily metastatic (N=4)	10.8±5.3	17.6±2.1*	12.2±6.4	16.2±3.4	10.1±6.7	14.3±3.4	8.1±3.8	11.7±2.0		
Spleen	3.6±0.9	8.1±2.7**	3.9±1.5	8.2±2.9**	3.6±2.1	6.9±2.6**	3.1±1.6	6.9±2.1**	2.4±1.1	4.8±1.9*
Remainder of body	71.2±4.7	65.7±4.2**	36.9±11.4	53.1±5.6**	14.5±7.6	37.7±5.6**	11.1±6.4	29.0±4.8**	7.5±5.6	19.3±2.6*

*p<0.05, **p<0.001; paired Student's t-test comparing OCTREO and NOCATE.

[a] In four patients with a heavily metastatic liver, liver retention was calculated separately.

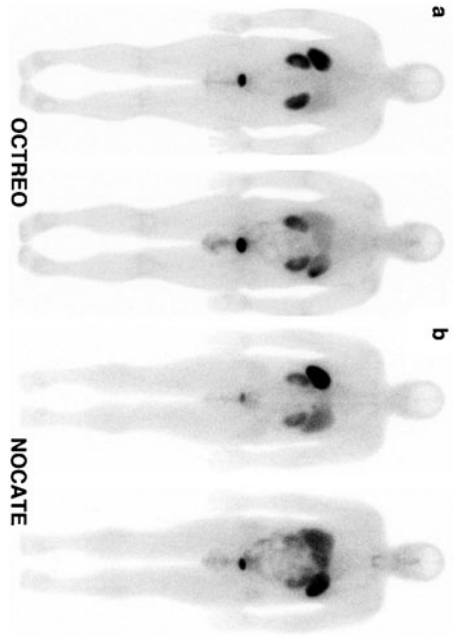

Fig. 2 WB scans (posterior and anterior views) at 4 h with OCTREO (**a**) and NOCATE (**b**) in a patient who was tumour-free at the time of scanning

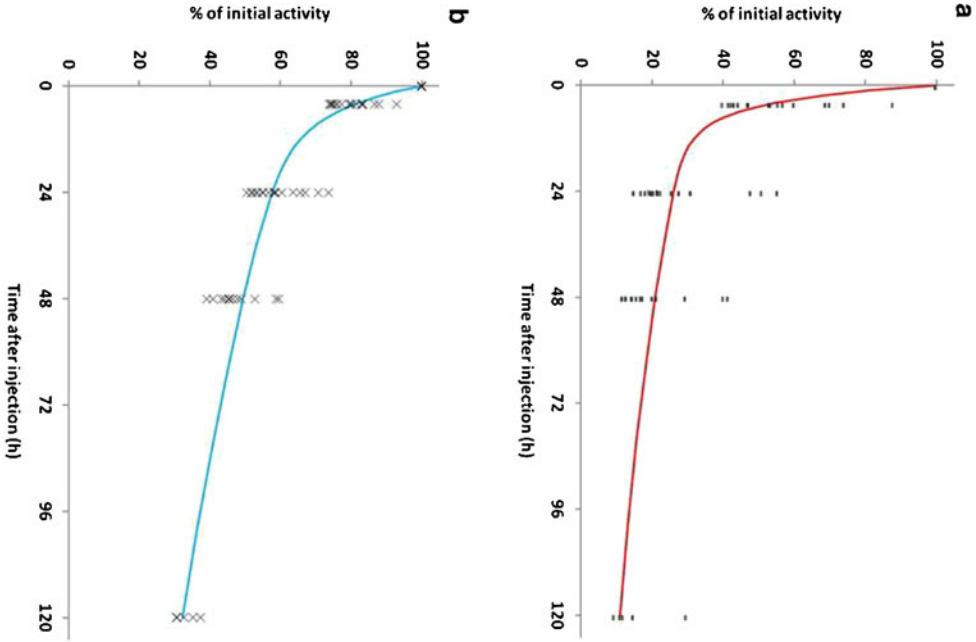

Fig. 3 WB activity in all patients corrected for the physical half-life of ^{111}In shown as percent of initial activity (reference scan) for OCTREO (**a**) and NOCATE (**b**). A biexponential function of activity was fitted to all combined values from individual patients shown for each scan time

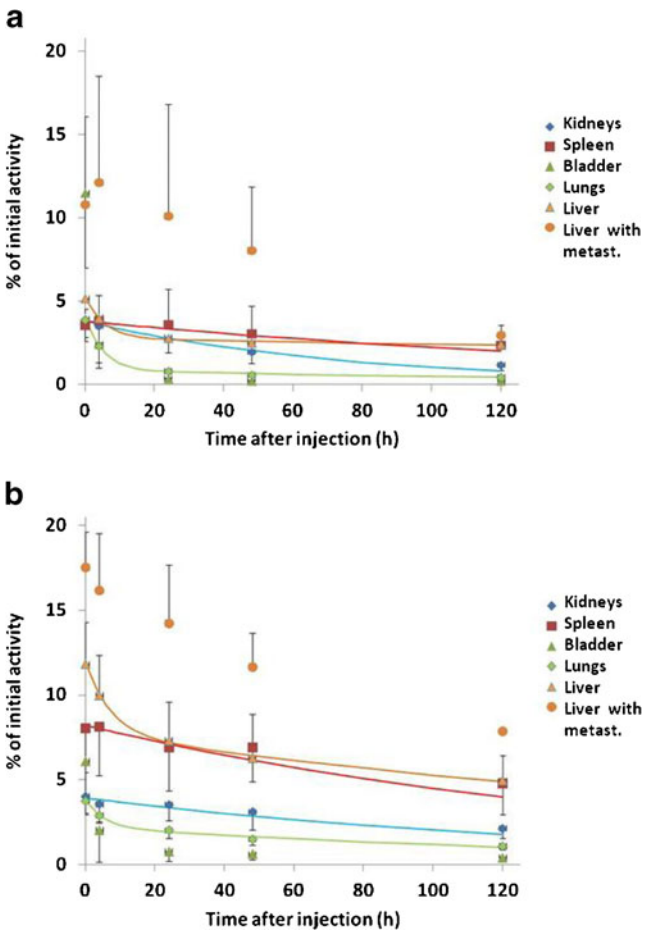

Fig. 4 Organ and bladder activities in all patients corrected for the physical half-life of ^{111}In shown as percent of WB activity at the time of the first scan (reference scan) for OCTREO (**a**) and NOCATE (**b**). Patient values are shown as mean ± SD for each scan time. The mean of the single exponential functions fitted to individual patient values are shown for the kidneys and spleen. Biexponential functions of activity were fitted to the combined patient values for the liver and lungs

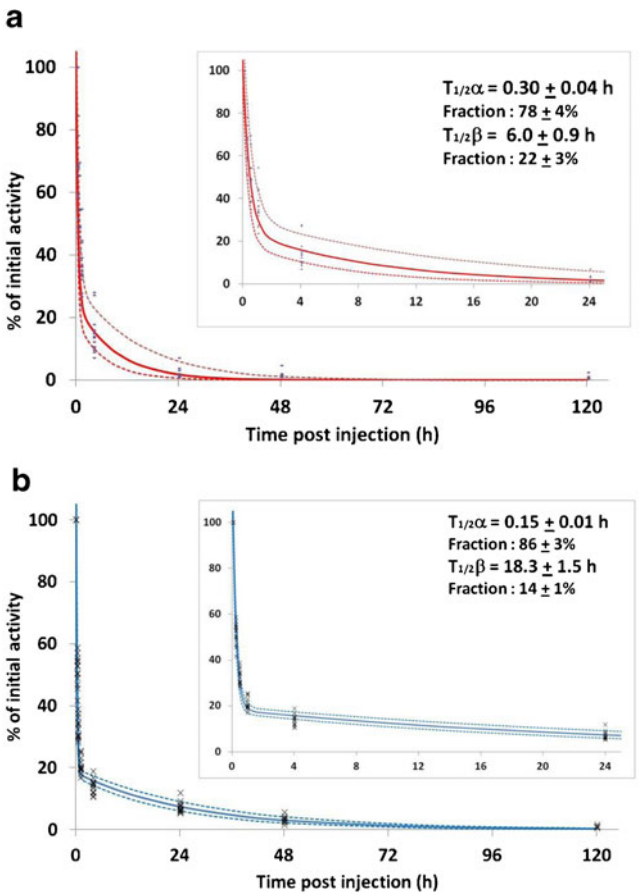

Fig. 5 Blood activity obtained in 14 patients expressed as percent of initial measured activity (at 5 min, set to 100 %) shown for OCTREO (**a**) and NOCATE (**b**). Biexponential functions fitted to the combined patient values of all blood drawings at all times show the effective half-lives. *Broken lines* indicate 95 % confidence intervals; *symbols* indicate all individual patient values

at 48 h and 120 h. In marked contrast, the NOCATE results were within a narrow range (Fig. 5b) showing a rapid decrease (α half-life) followed by a sharp transition into a long β half-life. The resulting 95 % confidence interval for OCTREO was thus larger than for NOCATE (Fig. 5). The summed blood α and β residence times (Table 3) of NOCATE were again much higher than those of OCTREO.

We checked whether a difference in cell-bound activity could explain the difference in blood clearance of OCTREO and NOCATE in seven patients (six men, one woman). For each patient, seven or eight paired blood samples were available both for OCTREO and NOCATE. Based on the haematocrit values, plasma activity was determined and compared with the measured blood activity. The results showed that 98.2±3.5 % of OCTREO activity was in the plasma while for NOCATE the percentage was slightly, but significantly, lower (96.8±4.1 %, $p<0.05$; results not shown).

Dosimetry of NOCATE and OCTREO

Dosimetry showed a consistently higher radiation dose from NOCATE than from OCTREO, except in the bladder where no increase was observed. For kidneys, the dose increase of NOCATE compared with OCTREO was slightly less marked than for other organs and the remainder of body (Table 4).

Comparison of the dosimetry of OCTREO in these patients with the ICRP data [9] revealed a higher value for the lungs. Overall, however, the calculated ED in our patients of 52 μSv/MBq correlated quite well with the ICRP value of 54 μSv/MBq.

Discussion

Despite a large difference in mean body weight between men and women (82 kg for men and 56 kg for women), the biodistributions of NOCATE and OCTREO (percentage of

Table 3 Measured effective half-lives of OCTREO and NOCATE in the whole body, tissues and blood obtained by fitting the tissue results to biexponential functions (giving α and β half lives) or single exponential functions (for spleen and kidneys)

Organ	Effective half-life (h)[a]		Fraction/organ (%)		Residence time (h) ($\tilde{A}_s/A_o$)		
	OCTREO	NOCATE	OCTREO	NOCATE	OCTREO (our results)	OCTREO (ICRP data)	NOCATE
Whole body α	2.5±0.6	3.8±1.1	67.7±6.3	34.2±3.3	18.8±3.6	–	41.3±2.1
Whole body β	35.9±5.9	42.8±1.6	32.3±4.2	65.8±2.2			
Lung α	3.35±0.3	3.3±1.8	3.3±1.1	1.7±0.3	0.7±0.2	–	1.4±0.2
Lung β	43.6±12.4	41.3±3.7	0.9±0.2	2.2±0.2			
Kidneys	29.9±7.5	46.0±10.9	3.8±1.0	3.9±1.1	1.6±0.5	2.8	2.4±0.7
Liver α	3.7±1.3	4.6±2.1	2.6±0.6	4.4±1.3	2.4±0.5	2.6	5.7±1.1
Liver β	59.8±8.1	49.2±7.1	2.8±0.4	7.7±1.0			
Spleen	43.8±10.7	40.8±5.7	3.8±1.4	8.2±2.8	2.4±1.2	2.3	4.8±1.9
Remainder of body[b]					10.7±6.4	6.9	26.1±6.2
Blood α	0.3±0.04	0.15±0.1	77.5±4.3	86.3±2.8	2.0±0.4	–	3.7±0.4
Blood β	6.2±0.9	18.5±1.5	22.5±2.4	13.7±0.5			
Red marrow[c]					0.2±0.1	–	0.3±0.1
Bladder[d]					0.8±0.3	1.7	0.6±0.1

[a] Results for the whole body, lungs, liver and blood were obtained by fitting all patient results combined to biexponential functions and are shown as estimated effective α and β half-lives with their respective fractions/organ ± the standard errors (uncertainty) propagated finally into the residence time; results for the kidneys and spleen were obtained by fitting single exponential functions to the patients individually and are shown as means ± SD for the effective half-lives, the fractions per organ and the residence times.

[b] Remainder residence time represents the WB residence time with the residence times of all the other organs and tissues analysed subtracted.

[c] Red marrow residence time was extrapolated from blood residence time according to the method of Wessels et al. [7] using a blood to marrow residence time ratio of 0.091.

[d] Bladder residence time was obtained using the bladder model with a filtration fraction of 1. The α and β biological WB half-lives with their respective fractions of OCTREO and NOCATE and a bladder voiding interval of 2 h were sequentially introduced into the bladder model and the α and β residence times summed.

injected activity per organ, blood and whole body) were very similar between the genders. Very similar residence times were thus observed in male and female patients for both NOCATE and OCTREO, and we therefore pooled the results for the genders. Our observations regarding OCTREO were in good agreement with the published ICRP dosimetry data [9]. It is worthy of note that the ICRP used identical residence times for men and women. NOCATE also gave similar results in men and women, further justifying the presentation of the results of both genders combined.

The dosimetry applied here was rather crude (without attenuation and scatter correction). However, the goal of this study was primarily to compare the biodistributions and biokinetics and the tumour-targeting capacity of NOCATE in comparison with OCTREO. Most patients did

Table 4 Tissue radiation doses (in micrograys per megabecquerel). For kidneys and spleen the values are means ± SD; for all other organs and tissues for which biexponential functions were fitted the values are mean ± standard error propagated from the residence times given in Table 3 The published ICRP data [9] are also shown)

Organ	OCTREO		NOCATE	NOCATE/OCTREO ratio
	ICRP 106	Our results	Our results	
Lung	23	46±13	99±14	2.2
Kidneys	410	252±79	404±117	1.6
Liver	100	97±20	226±43	2.3
Spleen	570	576±288	1150±455	2.0
Bladder	200	110±41	115±19	1.0
Red marrow	22	27±14	58±19	2.1
Remainder of body	24	29±17	64±15	2.2
Effective dose (μSv/MBq)	54	52	105	2.0
Effective dose equivalent (μSv/MBq)		87	169	1.9

not have a CT scan and none had a SPECT/CT scan, although some had a SPECT scan. Independent of the dosimetry method used, the comparison of NOCATE and OCTREO, obtained under identical conditions and under the same assumptions, remains valid, in our opinion.

Another drawback of this initial study of NOCATE in comparison with OCTREO is that data collection in these patients did not include measurement of faecal and urinary excretion of ^{111}In, and gastrointestinal activity was not determined since no SPECT/CT data were available. Retrospectively, considering the much higher uptake of NOCATE in the liver and spleen than of OCTREO, it would have been interesting to compare the NOCATE and OCTREO data by pharmacokinetic compartmental modelling. However, the entire protocol was quite demanding for these patients who underwent multiple scans and blood drawing. We therefore decided not to request urine and faeces collection, nor to perform SPECT/CT.

In the absence of measured data, we assumed for dosimetry purposes that the activity of NOCATE was also mainly eliminated via the kidneys, as is observed for OCTREO according to the ICRP. Indeed, as measured and modelled, faecal activity excretion on OCTREO scanning was rather low, representing only between 0.5 and 2 % of injected activity [10].

The biodistribution of NOCATE had been studied in male Lewis rats at 7 weeks of age [5]. While the NOCATE results in rats adequately predicted a long half-life in tissues including the kidneys, liver and spleen, the organ uptakes in %ID/g appear rather low in these animals weighing about 200 g compared with the human data reported here. The markedly higher effective dose of NOCATE than of OCTREO as observed here was thus not predicted from the animal studies.

A similar compound, DOTANOC labelled with ^{68}Ga, has been studied in humans [11]. Due to methodological differences (single photon WB scans versus PET), the results are not directly comparable. However, in that study the activity of DOTANOC seen in the liver and spleen was about half that of NOCATE in this study.

The observed differences between NOCATE and OCTREO cannot be explained conclusively. Different factors could theoretically explain our observations. The higher affinity of NOCATE than of OCTREO to different receptor subtypes could be responsible for a longer retention of receptor-bound NOCATE. However, the high uptake of NOCATE in normal liver and spleen probably cannot be explained in terms of affinity. In fact, while the uptake of NOCATE in normal liver is roughly double that of OCTREO, the differences between heavily metastatic livers and normal livers was very similar for both NOCATE and OCTREO at all scan times. These findings could suggest that the high uptake of NOCATE in normal liver and spleen is nonspecific. Another hypothesis suggests that the longer β half-life of NOCATE in blood could be due to binding to globular blood components. This hypothesis can be ruled out by experimental separation of globular blood components from plasma and separate radioactivity counting that showed that only a minor fraction of NOCATE was bound to globular blood components.

Conclusion

This comparative study of NOCATE and OCTREO, both radiolabelled with ^{111}In, showed a higher retention of NOCATE in all normal organs tested. The blood β half-life of NOCATE was also longer than that of OCTREO. The absorbed dose of NOCATE was roughly twice that of OCTREO.

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Conflicts of interest None.

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