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ARTICLE *in* EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING · MAY 2005

Impact Factor: 5.38 · DOI: 10.1007/s00259-004-1702-y · Source: PubMed

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Radiolabelling DOTA-peptides with ^{68}Ga

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Received: 28 May 2004 / Accepted: 9 September 2004 / Published online: 18 January 2005

Abstract *Purpose.* A new field of interest is the application of ^{68}Ga-labelled DOTA-conjugated peptides for positron emission tomography (PET). The commercially available or house-made generators require time-consuming and tedious handling of the eluate. Radiolabelling at high specific activities without further purification is not possible, while high specific activities are necessary for peptides that potentially display pharmacological side-effects. Here we present the practical aspects and the results of radiolabelling DOTA-peptides with a TiO_2-based commercially available ^{68}Ge/^{68}Ga generator.
Methods. Reaction kinetics and parameters influencing the incorporation of the radionuclide at the highest achievable specific activity were investigated. Since high finger doses were anticipated during handling of the high beta-energy emitter ^{68}Ga, finger dosimetric measurements were performed during radiolabelling and in vivo administration.
Results. Fractionated elution of the generator revealed that 80% of the radioactivity was recovered in 1 ml. Bi- and trivalent ionic contaminants that compete for the incorporation of the radionuclide were below 50 n*M*; thus further tedious and time-consuming purification was avoided. Radiolabelling was performed at pH 3.5–4. Plastic shielding (≥7-mm wall thickness) around the syringe during administration effectively eliminated the positrons. In rats $^{68}GaCl_3$ had slow clearance from blood, while ^{68}Ga-EDTA was rapidly cleared via the kidneys. Uptake of ^{68}Ga-DOTATOC in somatostatin receptor-positive tissues was high, with no significant difference between 1 and 4 h post injection.
Conclusion. DOTA-peptides for PET imaging can be labelled with ^{68}Ga up to specific activities of 1 GBq per nmol within 20 min, enabling the clinical application of peptides that display potential pharmacological side-effects.

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Keywords: Gallium-68 – Germanium-68 – Generator – DOTA – Radiolabelling

Eur J Nucl Med Mol Imaging (2005) 32:478–485
DOI 10.1007/s00259-004-1702-y

Introduction

Peptide receptor-targeted scintigraphy (PRS) and radionuclide therapy (PRRT) of receptor-positive tumours are currently being performed using DOTA-conjugated analogues of somatostatin (SS) such as octreotide (DOTA-TOC) [1] or octreotate (DOTA-tate)[1–6]. A new field of interest is the application of ^{68}Ga-labelled DOTA-conjugated peptides for positron emission tomography (PET), with concordant superior imaging technology, as has already been demonstrated in preliminary studies in patients [7–9]. Besides their use as PET imaging agents, these peptides might be a tool for research on individual SS receptor status and for optimal fine tuning of PRS and PRRT (in terms of timing and dosage). In a receptor binding study, several DOTA- and DTPA-conjugated SS analogues labelled with In, Ga or Y were compared: Ga-DOTATOC and Ga-DOTA-tate displayed the highest affinity for SS receptor subtype 2 [10]. When DOTATOC and DOTA-tate labelled with ^{67}Ga, ^{90}Y, or ^{111}In were then studied in an SS receptor-positive AR42J tumour-bearing mice model, the ^{67}Ga-labelled SS analogues displayed the highest uptake in SS receptor-positive tissues, the longest retention time and the lowest kidney uptake [10, 11]. The explanation for this finding lies in the difference in co-ordination of Ga^{3+} compared with In^{3+} and Y^{3+} in the DOTA complex [10, 12].

The ^{68}Ge/^{68}Ga generator has been under study since the 1970s, and gallium chemistry has been extensively reviewed [13–17]. The ^{68}Ga-eluate requires time-consuming (i.e. solvent extraction, ion exchange, pyrolysis and/or evaporation) and/or tedious handling (^{68}Ga is also a 1.8-MeV β^+ -emitter, 88% abundance) prior to radiolabelling [7–9, 18]. The reported maximal specific activity of the ^{68}Ga-labelled DOTA-peptides is below 50 MBq

per nmol and even then there is incomplete incorporation, necessitating further purification [7–9, 18]. We used a TiO_2-based commercially available $^{68}Ge/^{68}Ga$ generator, and specific activities of up to 1 GBq per nmol were achieved. With the technique described here even bioactive ^{68}Ga-DOTA-peptides with potential pharmacological agonistic side-effects can be studied in patients. Mariani et al. and Jonkhoff et al. reported the application of ^{67}Ga for PRRT as well as for PRS, since ^{67}Ga emits not only gammas but also Auger (0.1–8 keV) and internal conversion electrons (80–90 keV), as a result of which PRRT is effective [19, 20]. The application of ^{68}Ga-DOTA-peptides for PRRT has previously been suggested [10, 19].

In this study we discuss the practical aspects and present the results of the rapid preparation of ^{68}Ga-labelled DOTA-conjugated analogues of SS at high specific activities for preclinical and clinical investigations. Preclinical results are also presented.

Materials and methods

Physical characteristics and radiochemistry of the $^{68}Ge/^{68}Ga$ generator

We used $^{68}Ge/^{68}Ga$ generators (1,110 MBq, obtained from IDB Holland BV and originating from Obninsk, Russia; $t_{1/2}$ of ^{68}Ge and ^{68}Ga = 280 days and 68 min, respectively). The carrier of the generator is TiO_2, and it was eluted with 0.1 *M* Ultrapure HCl (Ultrapure HCl 30% was obtained from J.T. Baker, Deventer, The Netherlands). All chemicals were of the highest available grade. Fractionated elution of the generator was performed as follows: 24 fractions of 0.25 ml were collected and measured in a Veenstra VDC-405 dose calibrator. ^{68}Ga was quantified in the ^{18}F mode. The values measured in the ^{18}F mode were multiplied by (100/89): i.e. the abundance is 100% for ^{18}F and 89% for ^{68}Ga. The contribution of the 1.8-MeV positron (β^+ abundance: 88%) in this mode was found to be less than 5%. Elutions were performed at several times post former elution.

$$Elution efficiency(\%) = \frac{^{68}Ga activity at time of elution}{^{68}Ga activity on the column at time of elution} \times 100\%$$

After 24 h, the activity of ^{68}Ge is in equilibrium with the activity of ^{68}Ga; therefore, the elution efficiency ≥24 h post former elution is used to express the elution efficiency of the generator. ^{68}Ge in the fractions was quantified by measuring 511 keV. Note: in 24 h 1 MBq ^{68}Ga decays to 1 Bq ^{68}Ga.

$$Breakthrough(\%) = \frac{^{68}Ge activity}{^{68}Ga activity at time of elution} \times 100\%$$

For quantification, these fractions were also measured >24 h later in a well-type gamma counter (COBRA, Packard Instruments Co, Groningen, The Netherlands). Concentrations of Zn^{2+}, Al^{3+}, Ge^{4+}, Ga^{3+}, Ti^{4+}, Cu^{2+} and $Fe^{2+/3+}$ in these fractions were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES), with sequential measurement using a Varian Liberty (Bergen op Zoom, The Netherlands).

Radiolabelling and kinetics

Studies to optimise pH, temperature, time and kinetics were performed, measuring the percentage incorporation of the radionuclide, as described previously [21]. DOTATOC and DOTA-tate were obtained from BioSynthema (St. Louis, MO, USA) and H.R. Maecke (Basel, Switzerland), and were dissolved in 0.01 *M* acetic acid in Milli-Q water, with a final peptide concentration of 10^{-3} *M*. The peptide and the radioactivity were mixed with 1.25 *M* Na-acetate. pH was measured post labelling. Reactions in volumes up to 130 µl were performed in double-sealed MoBiTec vials (PCR thermocycler tubes, ITK diagnostics, Uithoorn, The Netherlands). Reactions in volumes up to 1.5 ml were performed in polypropylene or glass vials (Waters, Etten-Leur, The Netherlands). The vials were placed in a temperature-controlled heating block as described previously [21]. Instant thin-layer chromatography (ITLC) and C_{18} high-performance liquid chromatography (HPLC) were performed as described previously [22, 23]. In order to exclude the injection of particles or colloids, the $^{68}GaCl_3$-containing solutions were filtered over a 0.22 µm Millex-GV filter (VWR, Breda, The Netherlands). ^{68}Ga-EDTA was produced by adding 4 m*M* EDTA to $^{68}GaCl_3$ in a mol/mol ratio of 5,000 (EDTA over Ga^{3+}). The incorporation was determined by ITLC-SG and HCl-acidified saline pH 3.5; R_f=0.5–0.7 for free ionic $^{68}Ga^{3+}$ and R_f=1 for ^{68}Ga-EDTA. ^{111}In-DOTATOC was prepared as described previously [24].

Maximal achievable specific activity

As a basis for performance of clinical trials with ^{68}Ga-labelled bioactive peptides with potential pharmacological side-effects, studies on how to achieve the highest specific activity of these peptides were conducted, as described previously for DOTA-conjugated peptides such as DOTATOC and DOTA-tate [21]. Additional experiments were performed to confirm the values of the highest achievable specific activity. Known amounts of $^{69/71}Ga$ (Sigma-Aldrich, Zwijndrecht, The Netherlands) were mixed with $^{68}GaCl_3$ (37 MBq $^{68}Ga \equiv 3.6\times10^{-13}$ gram atoms Ga^{3+}). This was done in order to mimic the reaction conditions (at the same concentration of Ga^{3+} but with less radioactivity), as described previously [21]. The advantages hereof are: (1) a lowered dose (measured as skin dose [$H_p(0.07)$] and depth dose [$H_p(10)$], see section Health physics) and (2) avoidance of the handling of low amounts of peptide. We found that below 1 nmol of peptide, the reproducibility of the experiments decreases owing to an increase in sticking of these peptides to plastic, glassware, filters etc.

Animals and tissue distribution

Male pre-adolescent control and Lewis rats (200–300 g, Harlan-CPB, Austerlitz, The Netherlands) were kept under standard laboratory conditions (12 h light/12 h dark) and were given standard laboratory diet (Hope Farms, Woerden, The Netherlands) and water ad libitum. For the ^{68}Ga-DOTATOC experiments, control and SS receptor-positive CA20948 tumour-bearing Lewis rats were used. The experimental protocol adhered to the rules laid down by the Dutch Animal Experimentation Act and was approved by the Committee on Animal Research of the Erasmus MC Rotterdam. Between 3 and 10 MBq $^{68}GaCl_3$, ^{68}Ga-EDTA or ^{68}Ga-DOTATOC per rat was injected intravenously in the penis vein. Blood, spleen,

pancreas, adrenals, stomach, heart, kidney, liver, lungs, colon, sternum, muscle, pituitary and femurs were isolated at indicated times post injection (p.i.), and the concentration of radioactivity was measured in the well-type gamma counter LKB-282 compu gamma [21]. The injected peptide mass of DOTATOC per rat was 0.5 μg in 0.5 ml.

Transchelation

Transchelation of 37 MBq ^{68}Ga-DOTATOC was challenged in 1 ml containing 4 m*M* EDTA at pH 4. The labelling was checked up to 4 h following the start of radiolabelling. The mol/mol ratio of EDTA over $^{68}Ga^{3+}$ was up to 10^3 [21].

Health physics

Since ^{68}Ga emits not only gammas but also 1.8-MeV positrons, the skin dose and depth dose were measured as $H_p(0.07)$ (70 mg cm^{-2}) and $H_p(10)$ (1,000 mg cm^{-2}) [25]. Thermoluminescence dosimeters (TLD from NRG, Arnhem, The Netherlands) were irradiated by a 1-ml syringe containing 0.5 ml of a radioactive ^{68}Ga solution (at variable distances, MBq and time). The data were used to calculate personal dose rate equivalents per unit of activity (expressed as μGy MBq^{-1} s^{-1} at variable distances from the ^{68}Ga in 0.5 ml-containing syringes) for further calculations of hand and finger radiation dose, expressed in $H_p(0.07)$ and $H_p(10)$. Two different 1-ml syringes (Becton-Dickinson, Gouda, The Netherlands: models with 2.5 mm vs 1 mm wall thickness, density 0.9 and 1 g cm^{-2}, respectively) were used as models, with/without 4 mm Perspex extra shielding (density 0.9–1 g cm^{-2}). Monte Carlo calculations using the MCNP4C code [26] were applied on a simulation model with the above-mentioned characteristics. Both syringes were modelled free in air with dose (kerma) scoring regions of cylindrical shapes in the immediate vicinity (r<5 cm) and of spherical shapes further away. Dry air with a density of 1.29 kg m^{-3} was taken; the effect of lower density of moist air was neglected. Kerma free in air per cumulated activity in the syringe was calculated in cylindrical shells of 1 mm thickness up to 5 mm from the syringe's outer surface in the central 2 cm. Another cylindrical kerma scoring region of 2 mm thickness was situated at 3 cm from the syringe surface. The following kerma scoring region of t=2 mm was spherically shaped with r=8 cm, centred on the syringe. The positron spectrum of ^{68}Ga was taken from the ICRP38 database [27] and modelled in MCNP as if it were electrons. The annihilation photons of 511 keV were separately calculated using the same activity distribution in the liquid. The 3%/decay gamma rays of 1.077 MeV and the higher energy photons were modelled in a separate calculation. All calculations were performed with 2.5 million particle histories to limit the statistical fluctuations in the outcome to <1.5%. No attempt was made to explicitly model the TLDs [25].

The manual handling of the radioactivity was analysed for handling time, and distance from the source (from elution, radiolabelling, filtration, filling the syringe, the administration, etc) was registered. The highest value (in terms of time and distance) was found to be for the administration itself, with the index finger at ≈3 mm from the 0.5-ml source for 30 s.

Statistical analysis

Statistical analysis was performed using Student's t test (GraphPad, Prism4, San Diego, CA, USA). Statistical significance was defined at p<0.05.

Results

One hour after the former elution, the elution efficiency was 40–45%, and this value increased to 90–95% after 4 h (Fig. 1a). The first elutions of the generator resulted in a recovery of 90%, with a decrease to 60% after 8 months (>500 elutions). The fractionated elution showed a void volume of ±1.15 ml, and the fractions 6–9 (1 ml) contained 80% of the total ^{68}Ga recovered (Fig. 1b). The fractions 6–9 also contained ^{68}Ge, although at a lower ^{68}Ge concentration in comparison with the total eluate (fractions 1–24), and thus a relatively lower breakthrough (Fig. 1c).

In vitro stability studies of 37 MBq ^{68}Ga-DOTATOC in 1 ml 4 m*M* EDTA, pH 4 showed less than 1% transchelation, as measured up to 24 h after radiolabelling.

ICP measurements of Al^{3+}, $Fe^{2+/3+}$, Ge^{4+}, Zn^{2+}, Ti^{4+} and Cu^{2+} in the 0.25-ml fractions at 1, 4 and 24 h post former elution revealed a constant level of <50 n*M* for all, and in Milli-Q water and Ultrapure HCl, a level of <5 n*M*. The lower limit of detection for all metals was <0.5 n*M*.

The formation of ^{68}Ga-EDTA from EDTA and ionic $^{68}Ga^{3+}$ was completed (>95%) within 15 min at 20°C, while the formation of ^{68}Ga-DTPA never reached that level; therefore the in vivo studies were continued with EDTA.

The rate of incorporation of ^{68}Ga in DOTA-peptides was found to be pH dependent (Fig. 2a). There was no incorporation at pH 1, a slow start at pH 2.5, and completion of incorporation at pH 4 after 5 min at 80°C (Fig. 2b).

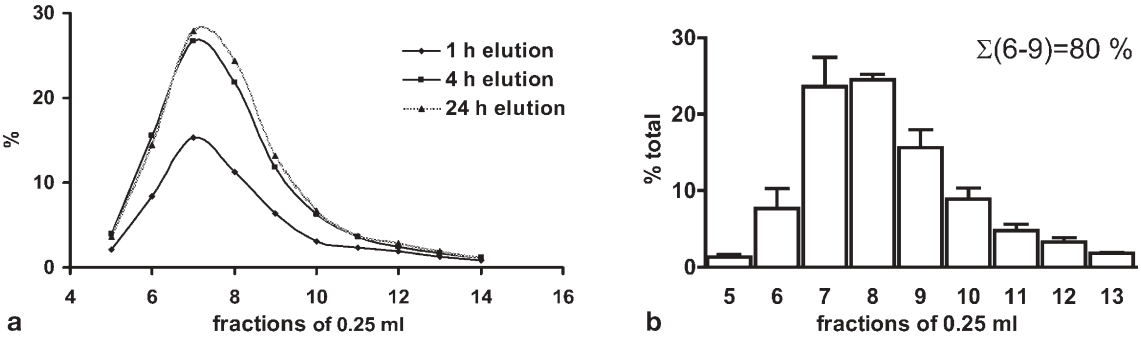
Maximal achievable specific activities were up to 1 GBq ^{68}Ga per nmol for DOTATOC and DOTA-tate and were confirmed with added $^{69/71}$Ga.

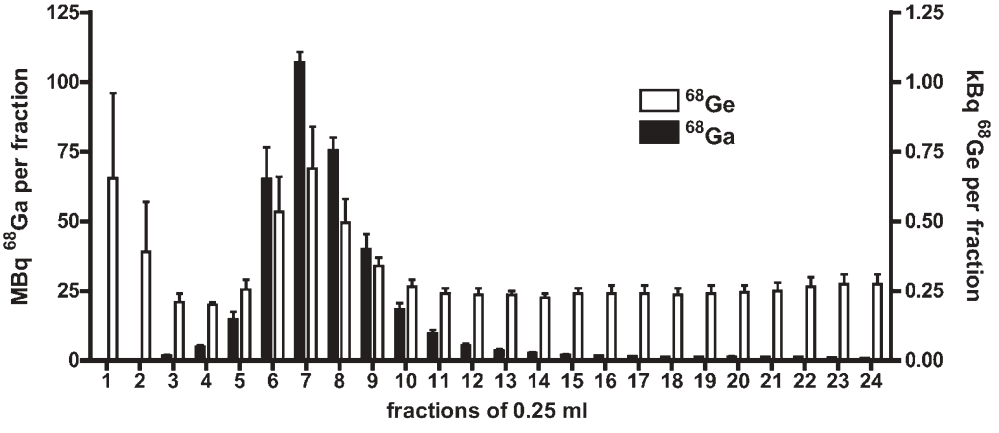
TLD measurements showed the beneficial effect of plastics in reducing the high-energy 1.8-MeV positrons: the radiolabelling of 555 MBq resulted in 60 μSv for $H_p(0.07)$ and $H_p(10)$. Administration per 10 MBq in rats was as follows:

- $H_p(0.07)$: 1,500 and 460 μSv with 1- and 2.5-mm wall thickness; 20 μSv with 4-mm Perspex
- $H_p(10)$: 20 μSv with 1- and 2.5-mm wall thickness and (still) 20 μSv with 4-mm Perspex.

These data were in accordance with the Monte Carlo calculations (Table 1).

$^{68}GaCl_3$ has a slow clearance from the blood compartment, with a concordant high concentration of radioac-





c

	fractions 6-9	fractions 1-24
^{68}Ge (kBq)	2,06 ± 0,6	7,49 ± 0,5
^{68}Ga (MBq)	286 ± 6	363 ± 3
Breakthrough (%)	0,**000**56	0,**00**205

Fig. 1. **a** Ingrowth of ^{68}Ga after fractionated elution of the ^{68}Ge/^{68}Ga generator at indicated time post prior elution, expressed as percentage of the steady state value of ^{68}Ga at 24 h. **b** Fractionated elution of the ^{68}Ge/^{68}Ga generator, 24 h post prior elution. The activity in 0.25 ml per fraction is expressed as percentage of the total activity. The void volume of the column is ±1.15 ml; the fractions 6–9 (∑1 ml) contain ca. 80% of the total activity. **c** ^{68}Ge and ^{68}Ga after fractionated elution of the ^{68}Ge/^{68}Ga generator 24 h post prior elution. ^{68}Ge breakthrough is expressed as % of ^{68}Ga and for fractions 6–9 (∑1 ml) and total eluate (∑6 ml). Experiments were performed in triplicate, at intervals of 1–2 days.

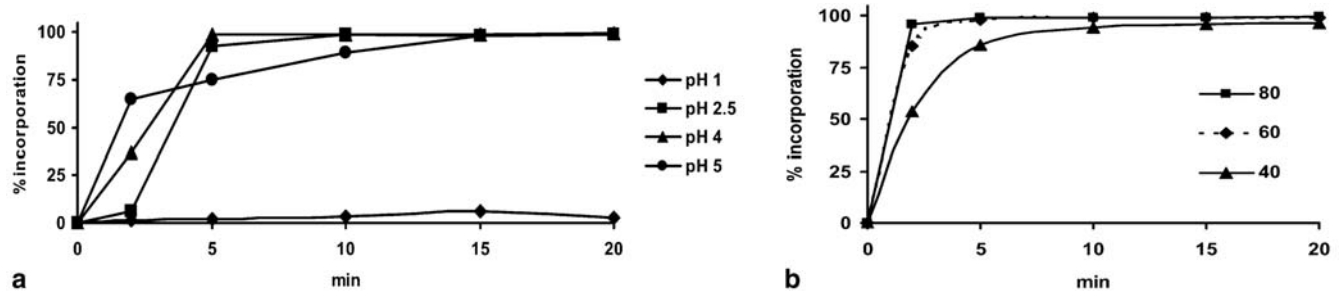


Fig. 2. **a** Formation of ^{68}Ga-DOTATOC as a function of pH and time at 80°C, as measured by the percentage incorporation of the radionuclide. Three different experiments were performed, with similar results. **b** Formation of ^{68}Ga-DOTATOC (at 10 MBq per μg DOTATOC in 120 μl at pH 3.5–4) as a function of temperature [40°C (*triangles*), 60°C (*diamonds*) and 80°C (*squares*)] and time, as measured by the percentage incorporation of the radionuclide.

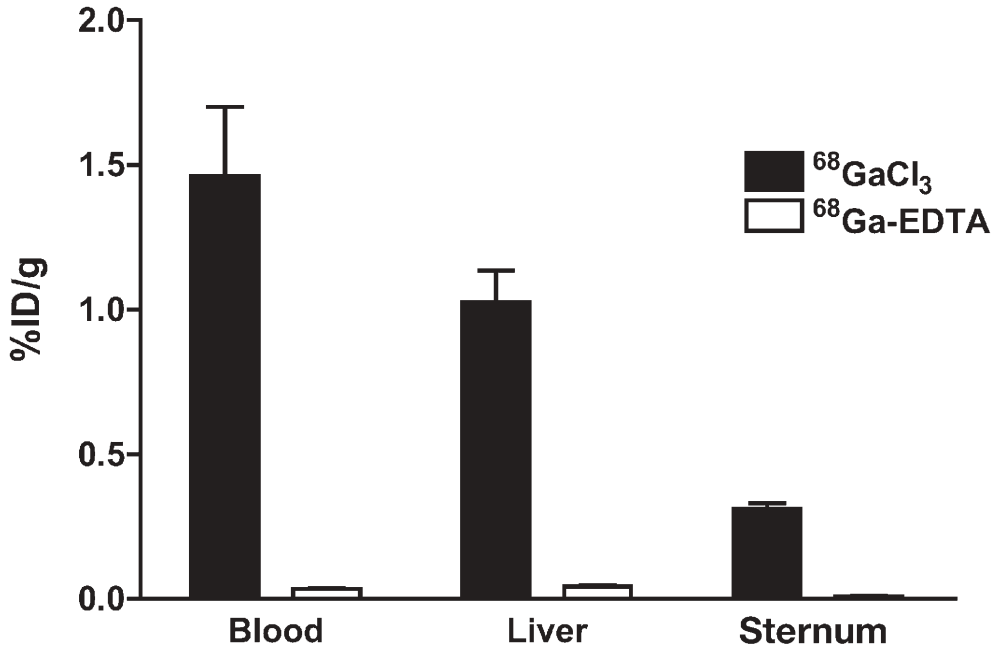


Fig. 3. Tissue distribution of $^{68}GaCl_3$ and ^{68}Ga-EDTA 4 h p.i. in rats (n=3), expressed as mean ± SD.

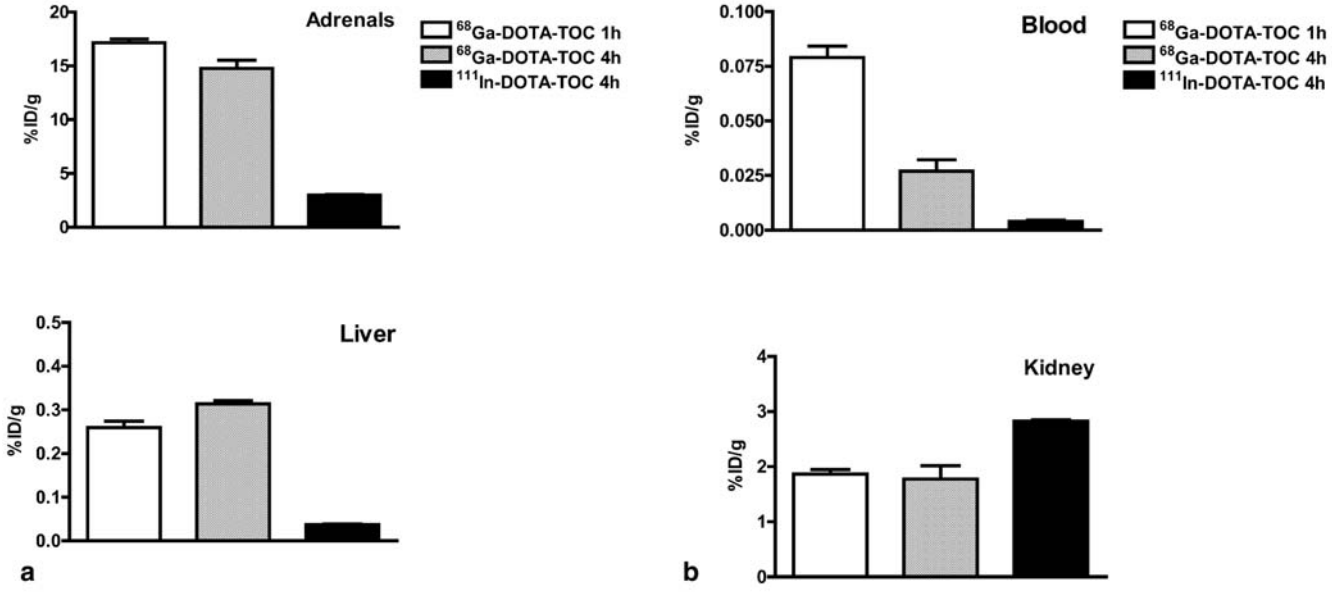


Fig. 4. a, **b** Tissue distribution of ^{68}Ga-DOTATOC at 1 and 4 h p.i. and ^{111}In-DOTATOC at 4 h p.i. in rats (n=3), expressed as mean ± SD.

Table 1. TLD measurements of 555 MBq-containing syringes with plastic walls of (A) 1, (B) 2.5 and (C) 6.5 mm thickness, expressed in Sv h^{-1}

	A	B	C
At surface	28	7.6	0.32
0.5 cm from φ	12	3.7	0.19
3 cm from φ	1.5	0.57	0.044
5 cm from φ	0.48	0.18	0.018

tivity in virtually all organs (Fig. 3, Table 2). ^{68}Ga-EDTA was rapidly cleared via the kidneys. The uptake of ^{68}Ga-DOTATOC in SS receptor-positive tissues, such as pancreas, adrenals, pituitary and CA20948 tumour, was high, with no significant difference in uptake at 1 and 4 h p.i. (Fig. 4, Table 2).

Discussion

The elution efficiency of the generator (see formulae) is expressed as the ^{68}Ge activity on the column; however, it is not simple to verify this activity. The elution efficiency decreased from 90% at the first elutions, to 60% after

Table 2. Tissue distribution of $^{68}GaCl_3$ and ^{68}Ga-EDTA at 4 h p.i., ^{68}Ga-DOTATOC at 1 and 4 h p.i. and ^{111}In-DOTATOC at 4 h p.i. in rats (n=3), expressed as mean ± SD

	$^{68}GaCl_3$ 4 h	^{68}Ga-EDTA 4 h	^{68}Ga-DOTATOC 1 h	^{68}Ga-DOTATOC 4 h	^{111}In-DOTATOC 4 h
Stomach	0.43±0.06	0.01±0.00	NA	NA	NA
Spleen	0.99±0.14	0.04±0.01	0.13±0.02	0.14±0.01	0.03±0.00
Lungs	0.68±0.11	0.03±0.01	NA	NA	NA
Muscle	0.10±0.04	0.00±0.00	0.01±0.00	0.01±0.00	0.01±0.00
Femur	1.02±0.13	0.03±0.00	0.14±0.03	0.16±0.03	0.05±0.01
Sternum	0.36±0.04	0.01±0.00	0.04±0.01	0.01±0.00	0.01±0.00
Pancreas	NA	NA	6.88±0.45	6.00±1.06	1.92±0.28
Pituitary	NA	NA	2.30±0.49	1.47±0.21	0.43±0.28
CA20948	NA	NA	2.90±0.69	2.53±0.97	1.63±0.69

NA not applicable

8 months and >500 elutions. With every elution there is some loss of ^{68}Ge owing to leakage. If one assumes a leakage of 7.5 kBq ^{68}Ge per elution (as presented in Fig. 1c), after 500 elutions the total leakage would be 3.75 MBq ^{68}Ge. With a 1,110-MBq generator this represents a loss of <1%, and thus does not explain the decrease in elution efficiency over time. Possibly the decrease is attributable to alteration in the column structure.

The concentration of contaminants competing with Ga^{3+} for incorporation in DOTA, such as Zn^{2+} and $Fe^{2+/3+}$, was low, at <50 n*M* for all 24 elution fractions at 1, 4 and 24 h post former elution. This low metal concentration enabled high specific activities to be achieved, i.e. up to 1 GBq per nmol DOTA-peptide.

The concentration of ^{68}Ge and ^{68}Ga in the 24 fractions showed different profiles (Fig. 1c): fractions 6–9 (1 ml) contained 80% of the ^{68}Ga activity; therefore the breakthrough (see formulae) calculated for fractions 6–9 and fractions 1–24 differed (Fig. 1c).

The reaction kinetics for the incorporation of the radionuclide is inversely related to the pH [28]. Hence different critical (for colloid formation) pH values were reported: 3 and 5.1 with ^{68}Ga at concentrations of 370 and 37 MBq per ml [13, 14], respectively. Therefore, we calculated the critical pH values with a solubility product (components expressed in M/L) of 7.1×10^{-36} [13] and found pH 5.3 and 4.95 for 100 and 1,000 ^{68}Ga MBq/ml, respectively, and pH 4.6 and 4.2 for 100 and 1,000 ^{67}Ga MBq/ml, respectively. As a compromise between solubility and kinetics, the studies were performed at pH 3.5–4, which resulted in complete incorporation of Ga^{3+} in 5 min at 80°C (Fig. 2b), up to specific activities of 1 GBq per nmol. This in contrast to other studies with specific activities below 50 MBq per nmol with incomplete incorporation, necessitating further purification [7, 8]. Recently, Meyer et al. [18] reported on a TiO_2-based generator from Obninsk, including an automatic procedure for concentration and purification by column chromatography. However, the radiolabelling procedure at specific activities below 50 MBq per nmol still required further purification. In their procedure an accidental ^{68}Ge breakthrough could be avoided—an unwanted event that in our procedure would be detected owing to incomplete incorporation or after decay of ^{68}Ga. However, we have not experienced breakthrough (we now have experience with three generators), and even without the extra purification, breakthrough is constantly low in our setting (Fig. 1c).

Bioactive peptides with potential pharmacological side-effects, such as bombesin, can be injected in patients at a rate of 0.1 nmol min^{-1} [29]. With the technique described here, these peptides, radiolabelled at a specific activity of 1 GBq per nmol and with a supposed dose of 200 MBq (equals 0.2 nmol), clinical administration will take 2 min.

The selection of radiolabelled DOTA-peptides available for PRRT can, therefore, now be based on the results of scans with these ^{68}Ga-DOTA-peptides in each patient. Thus factors that influence optimal target uptake, such as the choice of the best radioligand and concordant timing and dosage (in megabecquerels and nanomoles), can now be studied in each patient. Although the thermodynamic stability constants for both EDTA and DTPA for Ga^{3+} are very high (21.7 and 23.3, respectively) [13], the formation of ^{68}Ga-DTPA under our conditions was found to be low, in contrast to the formation of ^{68}Ga-EDTA; therefore we continued our studies with ^{68}Ga-EDTA. Moreover, the addition of DTPA prior to quality control of $^{66/67/68}$Ga-labelled products under acidic conditions can be replaced by addition of EDTA. Deferoxamine (DFO) as a binder for Ga^{3+} ions was not studied as an alternative to DTPA since it is questionable whether Ga-DFO can be successfully used at low concentrations [30]. Handling high beta-energy emitters such as ^{68}Ga and ^{90}Y requires low atomic number shielding. Since the $H_p(0.07)$ and the $H_p(10)$ of the 0.5 ml ^{68}Ga-containing plastic syringes with a total wall thickness of 7 mm plastic were identical, it is likely that the betas are effectively eliminated. ^{68}Ga-EDTA cleared rapidly via the kidneys, while $^{68}GaCl_3$ cleared slowly with a concordant high concentration of radioactivity in virtually all organs (Fig. 3, Table 2).

The uptake of ^{68}Ga-DOTATOC in SS receptor-positive tissues was rapid. The radioactivity concentration in SS receptor-positive tissues did not differ significantly at 1 and 4 h p.i.; only the clearance from blood was significant, with blood values halving between 1 and 4 h p.i. As a result, the already high target to blood ratio at 1 h p.i. increased at 4 h p.i.

The uptake of ^{68}Ga-DOTATOC in SS receptor-positive tissues, such as pancreas, adrenals, pituitary and CA20948 tumour, was the highest that we have encountered in this rat model [24, 31], while uptake in the kidney was the lowest (Fig. 4, Table 2). These results confirm the data obtained in mice [10] and patients [7–9].

Besides gammas, ^{67}Ga also emits Auger (0.1–8 keV) and internal conversion (80–90 keV) electrons and might therefore be suitable for PRS and PRRT [10, 19]. The current PRRT clinical trials with ^{90}Y-DOTATOC and ^{177}Lu-DOTA-tate have bone marrow and kidney as the dose-limiting organs. The reported reduction in kidney retention and the concordant higher tumour uptake of $^{67/68}$Ga-DOTA-peptides enhances the potential role of ^{67}Ga-DOTATOC and ^{67}Ga-DOTA-tate in PRRT.

The general conclusions of the data presented here are:

1. ^{68}Ga-DOTA-peptides for PET imaging can be prepared rapidly (<20 min).
2. High specific activities were achieved.
3. Bioactive ^{68}Ga-DOTA-peptides with potential pharmacological side-effects can now be applied clinically.
4. Tedious handling of the eluate is reduced.
5. Plastic shielding of the syringe during administration is strongly recommended.

Acknowledgements. We thank the working group WG3 from the COST B12 European Community for stimulating discussions. We are grateful to Drs. F. Moet, N. Verstraeten and R. van der Zwart (Mallinckrodt Medical) for the ICP measurements.

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