Cyclotron produced ^{67}Ga for preparation and clinical application of ^{67}Ga-DOTATOC

K. Zhernosekov[1], Aschoff[2], D. Filosofov [3], M. Jahn[1], M. Jennewein[1], P. H-J. Adrian[2], H. Bihl[2], F. Rösch[1]
[1]Institut für Kernchemie, Johannes Gutenberg-Universität, D-55128 Mainz, Germany; [2]Klinik für Nuklearmedizin und PET-center, D-70022, Stuttgart, Germany; [3]Joint Institute of Nuclear Research, LNP, 141980 Dubna, Russia

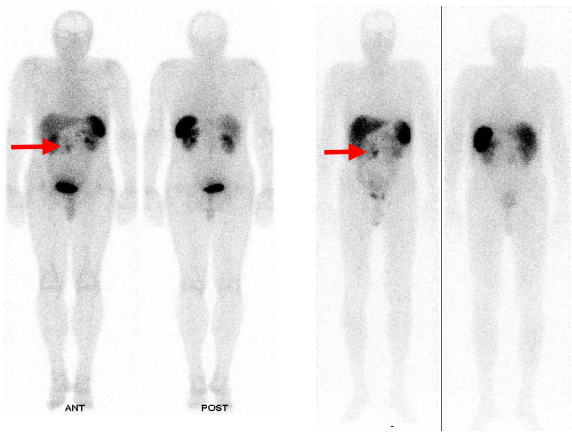
Introduction: Radiogallium labelled DOTA-conjugated somatostatin analogues (DOTA-octreotides) are very promising for the diagnoses of somatostatin receptor-expressing tumours due to the high binding affinity to the human somatostatin receptor subtype 2 and an improved pharmacology *in vivo* (Hofmann et al., 2001). Especially if the generator-produced positron emitter ^{68}Ga is used for labelling, excellent visualisation with PET/CT can performed. However, SPECT is still more widely available and for routine diagnostic radioindium labelled ^{111}In-DTPA-octreotide (Octreoscan) is used. ^{67}Ga (EC, T½ = 78.3 h) is a useful SPECT isotope. To advance this radionuclide for clinical application, in this work we evaluate commercially available ^{67}Ga for preparation of injectable ^{67}Ga-DOTATOC and used it in a pilot study of human somatostatin receptor-expressing tumour imaging with SPECT/CT.

Experimental: Only analytical-reagent grade chemicals and Milli-Q water (18.2 MΩ·cm) were used for all labelling reactions. About 1.0 GBq of ^{67}Ga(III) was obtained from Cyclotron Co., Obninsk Russia in 0.1 M HCl solution with specific activity not less than 370 MBq/µg (25 MBq/nmol). A ^{67}Ga activity in 0.1 M HCl solution was used directly for labelling in 1 ml of HEPES buffer pH ~ 3.7 in a 2 ml reaction vessels (PP, Brand). The radioactivity concentration was about 500 MBq/ml. The reaction mixture was kept at about 98°C for 30 minutes. For quality control HPLC (Machery Nagel column, Nucleosil 5 C18-AB, 250×4 mm; eluent: 20% AcCN, 80% TFA - 0.01 % in H_2O, 1 ml/min; RT ~ 9 min) was applied.

The theoretical (maximum) specific activity of ^{67}Ga-DOTATOC is 1.48 GBq/nmol. However, in our case labelling was performed after about 1.5 of half-life of ^{67}Ga from the end of its production and processing. ^{67}Ga decays to stable ^{67}Zn. Therefore, even if the content of $^{67/68}$Zn(II) from the irradiated zinc target is negligible, the amount of this stable decay product presented in the system is higher than that of the hot-atoms: $[^{67}Ga] \leq 1.5 \cdot [^{67}Zn]$.
Divalent zinc was found to be a competitor for incorporation of radionuclides in DOTA with a strong effect already at concentrations of 1 µM (Breeman et al., 2003). In this work labelling was performed at activity concentrations of 500 MBq/ml, resulting in 0.34 µM of gallium and not less than 0.68 µM of zinc concentrations. In this context, for complete incorporation of ^{67}Ga(III), corresponding excess of the ligand is necessary to compensate the content of Zn(II). Following this assumption, a specific activity of about 520 MBq/nmol only could be expected.

Results: Specific activities of ^{67}Ga-DOTATOC up to ~ 214 MBq/nmol could be achieved. The experimentally obtained value is only a factor 2.4 less than the theoretically expected one. It confirms the high chemical and radiochemical purity of the commercially obtained isotope and its applicability without additional purification procedure.
For *in vivo* studies ^{67}Ga-DOTATOC was used with a specific activity of 70 MBq/nmol. Cold ligand was added to the reaction mixture in order to stabilise the radiolabelled peptide in the system.
The reaction mixture was passed through a small C18 cartridge (Phenomenex Strata-X Tubes, 30 mg), providing quantitative recovery of the peptide on RP. After washing the cartridge with 5 ml H_2O (Aqua ab iniectabilia), the ^{68}Ga-labelled peptide was recovered with 200 – 400 µl of pure ethanol. The ethanol eluate containing the pure ^{68}Ga-DOTATOC was dissolved in 5 – 10 ml 0.9 % saline solution and sterilised by filtration through a 0.22 µm membrane filter.
Two patients with positive somatostatin receptor scintigraphy (Octreoscan®) were involved in the pilot study injecting ~ 230 MBq of ^{67}Ga-DOTATOC. Prior to ^{67}Ga-DOTATOC application, each patient had received 180 MBq of ^{111}In-octreoscan one week before. All metastases detected with ^{111}In-DTPAOC could be visualized with ^{67}Ga-DOTATOC as well. Scans of ^{67}Ga-DOTATOC (SPECT/CT) were performed in less then 4 h p.i. to generate excellent images with higher tumour to background ratio compared to ^{111}In-DTPAOC images (Fig. 1). The presence of only faint renal ^{67}Ga-DOTATOC uptake constitutes a further favourable characteristic of this radiolabelled peptide (Zhernosekov et al., 2005)

Figure 1. Planar scintigraphy: ^{111}In-DTPAOC 4 h p.i. (on the left); ^{67}Ga-DOTATOC 3 h p.i. (on the right)



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