Can gallium-68 compounds partly replace ^{18}F-FDG in PET molecular imaging?

Margarita Pagou, Imene Zerizer, Adil AL-Nahhas

Professor Adil AL-Nahhas, Department of Nuclear Medicine, Hammersmith Hospital, Imperial Healthcare Trust, Du Cane Road, London W12 0HS, United Kingdom, Tel.: 0044 208 3834923, Fax: 0044 208 3831700 E-mail: adil.al-nahhas@imperial.nhs.uk

Hell J Nucl Med 2009; 12(2): 102-105 • Published on line: 28 May 2009

Abstract

The development of gallium-68 -1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (^{68}Ga-DOTA) compounds was made possible due to the chemistry of ^{68}Ga, which matches the pharmacokinetics of many peptides, specially the chelators DOTA and DOTA-derivatives with the formation of stable ^{68}Ga (3+) complexes. The availability of this tracer from a germanium-68–gallium-68 generator with a relatively long half-life makes it attractive to use in busy nuclear medicine departments, particularly those with limited access to cyclotrons. The recent clinical experience with ^{68}Ga-peptides includes imaging neuroendocrine tumours particularly carcinoid, as well as neuroectodermal tumours such as phaeochromocytoma and paraganglioma. In vitro and animal testing are still progressing alongside clinical studies, with promising results in the use of ^{68}Ga-DOTA-rhenium-cyclized alpha-melanocyte stimulating hormone (MSH) and ^{68}Ga-DOTA-napamide (NAP) in melanoma, ^{68}Ga-DOTA-PEG(4)-BN(7-14) (PESIN) for the imaging of bombesin receptor-positive tumours and ^{68}Ga-ethylene dicysteine-metronidazole (EC-MN) for imaging tumour hypoxia. In addition to tumours, ^{68}Ga-DOTA peptide inhibitor of vascular peptide protein 1(VAP-P1) is being assessed for imaging inflammatory reaction. An additional value following a positive scan is the use of beta emitters labelled to the same peptides for radionuclide treatment. *In conclusion*, the recent introduction of ^{68}Ga-peptides, made available by a convenient ^{68}Ga/^{68}Ge generator, could greatly contribute to the management of a wide range of clinical conditions including tumours and inflammation.

Keywords: Gallium-68 – Peptides – Neuroendocrine tumours – Somatostatin receptors

Radiopharmacy of gallium-68(^{68}Ga) peptides

Gallium-68 is a metallic positron emitter that can be produced from a generator system consisting of an inorganic and organic matrix immobilizing the parent radionuclide germanium-68 (^{68}Ge), which has a long half-life of 271 days [1]. A variety of mono- and bifunctional chelators have been developed which allow the formation of stable ^{68}Ga(3+) complexes and convenient coupling to biomolecules [2]. Gallium-68 has suitable physical properties with a high positron yield reaching 89% of all disintegrations, and its half life of 68min matches the pharmacokinetics of many peptides and other small molecules owing to a fast clearance, quick diffusion and target localization [3].

In the last decade there has been a significant increase in the development of radiolabelled peptides for diagnostic applications, especially due to simplified methods of purification. Peptides have fast clearance, rapid tissue penetration, and low antigenicity and can therefore be produced easily and inexpensively [4].

Receptor imaging was inspired by endogenous somatostatin that consists of a family of a 14- and 28-amino acid peptide – subtypes bold (SS14, SS28) [5]. The synthetic octreotide is an eight-residue somatostatin analogue [6] and octreotate is another analogue, carrying a C-terminal CO(2)H (Thr) instead of the CH(2)OH (threoninol) group [7].

Recent developments include the use of DOTA which is a 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid and newer DOTA-derivatives, bifunctional chelate macrolides available for coupling to peptides and also capable of forming stable complexes with radiotracers of the metal group such as ^{111}In, ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{90}Y and ^{177}Lu [8, 9]. The DOTA-linked peptides include DOTA-octreotate (DOTATOC) and (DOTA[-2-Na^{1}-Tyr^{3}-Thr-NH$_2$^{8}]-octreotide) (DOTA-lanreotide), (DOTA-1-Nal-octreotide) (DOTANOC) and (DOTATATE) (DOTA-Tyr^{3}Thr^{8}-octreotide) [9-11].

Somatostatin receptors

The five different somatostatin receptor subtypes (SSTR1-5) that have been characterized are encoded by five genes, which are localized on separate chromosomes. SSTR1-5 exhibit high binding affinity to the natural ligands SS-14 and SS-28. Only receptor subtypes SSTR2 (which can be further divided into SSTR2A and SSTR2B), SSTR5 and to a lesser extent subtype SSTR3 have a high affinity for commercially available synthetic analogues and even these differ in their affinity for the various analogues. Somatostatin receptors are expressed in many tissues, and multiple subtypes often coexist in the same cell. Some of these receptors are overexpressed in several human tumours, especially neuroendocrine tumours (NET) and their metastases [5, 12-14].

The chemical structure, different charges and hydrophobicity of DOTA-somatostatin tracers, as well as the coordination geometry of the radiometal complex, have a significant influence in SSTR affinity profiles. For instance, DOTATOC, DOTA-octreotate and DOTATATE are able to induce SSTR2 internalization. DOTA-lanreotide has high affinity for SSTR5, while DOTANOC is relatively recently introduced and shows a high affinity for SSTR2, SSTR3 and SSTR5 [15-17].

Clinical experience with ^{68}Ga peptides

Hoffmann and colleagues (2001) were the first to demonstrate that ^{68}Ga-DOTATOC PET could identify all lesions in eight patients with carcinoid tumours, whereas indium-111 (^{111}In) octreotide identified 85% of tumours. Quantitative analysis showed higher tumour to non-tumour ratios with low kidney accumulation [18].

Another comparison between the two radiopharmaceuticals in a small group of 4 patients with metastatic NET showed that ^{68}Ga-DOTATOC was better in demonstrating smaller lesions with low tracer uptake, especially with tumours bearing only a low density of somatostatin receptors [19]. In a larger series of 84 patients with known or suspected NET ^{68}Ga-DOTATOC had a sensitivity of 97%, a specificity of 92% and an overall accuracy of 96% [20].

Semi-quantitative analysis of ^{68}Ga-DOTATOC showed a variable standardized uptake value (SUV) range (0.877-28.07 mean: 8.73), while dynamic quantitative kinetics evaluation (k_1: receptor binding k_3: cellular internalisation and V_b: fractional blood volume) could provide information that may prove vital for the assessment of the therapeutic result after ^{90}Y-DOTATOC [21].

Most of the studies performed were in patients with carcinoid though ^{68}Ga-DOTATATE was also positive in gastrinoma and insulinoma [22] as well as in malignant abdominal paraganglioma [11].

In our initial report of the use of ^{68}Ga-DOTATATE in neuroectodermal tumours, we reported on a group of five patients who had previously undergone surgical resection of histologically proven malignant phaeochromocytoma and subsequently presented with clinical and biochemical signs of recurrence. Gallium-68-DOTATATE was positive in all patients while only three patients had positive iodine-123 metaiodo benzyl guanidine (^{123}I-MIBG). The SUV(max.) for the positive lesions ranged from 4.6 to 10.4 indicating good tumour to background ratio [23] (Fig. 1).

Milker-Zabel et al. (2005) reported the first results of the use of ^{68}Ga-DOTATOC in meningiomas in three patients [24]. The diagnosis of meningiomas by computerized tomography (CT) and magnetic resonance imaging (MRI) is often difficult, especially at the base of the skull, and additional methods for the characterization of intracranial lesions are needed to avoid a hazardous biopsy. Meningiomas express high concentration of SSTR2 and are a good model for imaging with ^{68}Ga-DOTATOC. The same group went on to evaluate kinetic parameters in this disease, which allowed a more comprehensive assessment of tumour biology [24]. Most recently the value of ^{68}Ga-DOTATOC prior to fractionated stereotactic radiotherapy (FSRT) in 26 patients has been assessed. The radiolabelled peptide offered additional information concerning tumour extension, with improvement of target definition for FSRT [25].

Preclinical studies with ^{68}Ga labelled compounds

The development of clinical application of ^{68}Ga peptides is unusual in that it preceded pre-clinical animal work. However, the latter is still on-going and in vitro and animal testing with various chelators and compounds are still progressing alongside clinical studies.

It has been demonstrated that gallium ^{67}Ga- and ^{68}Ga-DOTA-octapeptides have distinctly better pre-clinical pharmacological performances than ^{111}In-labelled peptides, especially on SSTR2-expressing cells and the corresponding animal models [3]. Gallium-68 and DOTA chelate stably labelled with 3 different forms of antisense oligonucleotides targeting activated human K-ras oncogene was shown to be a convenient approach for in vivo imaging and quantification of oligonucleotides biokinetics in living animals [26].

In melanoma, ^{68}Ga-DOTA-rhenium-cyclized alpha-melanocyte-stimulating hormone (alpha-MSH) analogue (DOTA-ReCCMSH (Arg11)) is considered a promising agent for early detection in mice bearing B16/F1 melanoma tumour [27]. Likewise, ^{68}Ga-DOTA-NAPamide, a short linear alpha-melanocyte-stimulating hormone analogue, is superior to ^{111}In-DOTA-MSH in targeting melanocortin type 1 receptor in murine models of primary and metastatic melanoma [28].

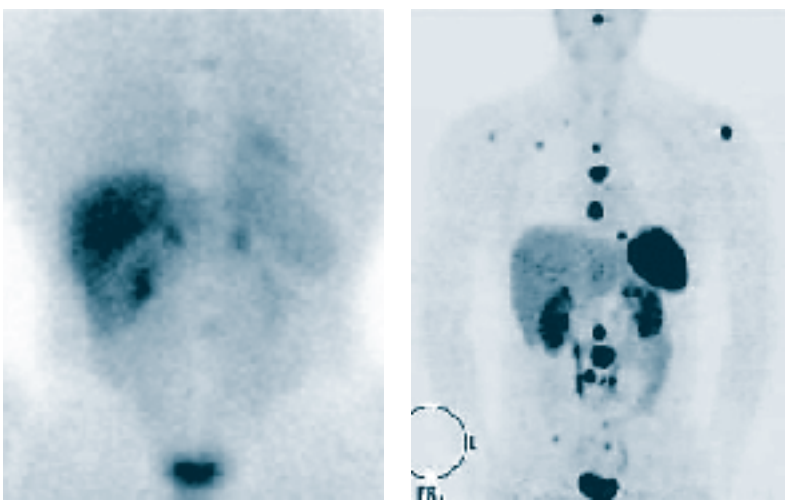

Figure 1. Comparative study in a patient with malignant paraganglioma. **A**: Posterior planar image with ^{123}I-MIBG showing faint uptake in 3 lesions in the spine. The adrenals are noted as prominent but normal structures. **B**: MIP image of ^{68}Ga-DOTATATE showing numerous well-defined and intense lesions involving the base of the skull, left shoulder, multiple vertebrae, mediastinum as well as multiple soft tissue lesions.

Bombesin (BN) analogues have become a promising class of ligands, as gastrin-releasing peptide (GRP) receptors, a subtype of BN receptors, were found to be overexpressed in invasive primary prostate carcinoma and associated lymph nodes, breast tumours and gastrointestinal stromal tumours (GIST) [29]. A recent study used DOTA-PESIN , a DOTA-conjugated bombesin derivative, designed for the imaging and targeted radionuclide treatment of bombesin receptor-positive tumours. The fast background clearance of ^{68}Ga-DOTA-PESIN peptide was considered a great advantage for this tracer [30].

In vitro cellular uptake of ^{68}Ga metronidazole (MN) with ethylenedicysteine (EC) as a chelator, and its biodistribution in breast-tumour bearing rats have indicated that it is feasible to use this tracer for assessment of tumour hypoxia, known to affect response to cancer treatment [31].

Overexpression of multidrug resistance (MDR1) P-glycoprotein (Pgp) remains an important barrier to successful chemotherapy in cancer patients and impacts on the pharmacokinetics of many important drugs, thus evoking a need to non-invasively understand Pgp transport activity in vivo. Molecular imaging of the functional transport activity of MDR1 Pgp with ^{67}Ga ^{68}Ga-[3-ethoxy-ENBDMPI] may enable non-invasive single photon emission tomography/positron emission tomography (SPET/PET) monitoring of the blood-brain barrier, chemotherapeutic regiments, and MDR1 gene treatment protocols in vivo [32, 33].

In the assessment of infection and inflammation, ^{68}Ga-DOTAVAP-P1, a peptide inhibitor of vascular adhesion protein 1/semicarbazine sensitive amine oxidase (VAP-1/SSAO), is a promising target molecule for the assessment of inflammatory reaction in healing bones [34]. Other studies have suggested a role for ^{68}Ga in imaging of experimental osteomyelitis due to staphylococcus aureus [35-37].

Peptide receptor radionuclide therapy

An inherent added advantage to the diagnostic approach with labelled peptides is its therapeutic implication for treatment. When the diagnostic scan is positive, the peptides can be labelled with therapeutic radionuclides such as yttrium-90, lutetium-77 or rhenium-188 to perform peptide receptor radionuclide treatment.

In conclusion, the use of a ^{68}Ge-^{68}Ga generator that can provide constant supply of ^{68}Ga with a half-life of 271 days provides the basis for convenient, easy use of this radionuclide for more than one year. The cost of the generator is variable depending on manufacturers and, when adequately used, is cost effective compared to other SSR imaging agents. Labelling of DOTA-related peptides can be performed in a very short time, allowing for excellent imaging of neuroendocrine and neuroectodermal tumours. On-going experimental work suggests that labelling other molecules for use in imaging other tumours and infection is feasible. When used for a large number of patients with different tumours, the cost of ^{68}Ga PET is reasonable particularly for centres with limited or no access to cyclotrons. The commercial availability of ^{68}Ge/^{68}Ga generator will encourage further preclinical research and clinical studies in the near future. Nevertheless, and due to pharmaceutical legislation, hard work is necessary before ^{68}Ga radiopharmaceuticals could attain widespread application in nuclear medicine practice.

Bibliography

1. Maecke HR, Andre JP. ^{68}Ga-PET radiopharmacy: A generator-based alternative to ^{18}F-radiopharmacy. *Ernst Schering Res Found Workshop* 2007; 62: 215-242.
2. Fani M, Andre JP, Maecke HR. ^{68}Ga-PET: a powerful generator-based alternative to cyclotron-based PET radiopharmaceuticals. *Contrast Media Mol Imaging* 2008; 3: 67-77.
3. Antunes P, Ginj M, Zhang H et al. Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? *Eur J Nucl Med Mol Imaging* 2007; 34: 982-993.
4. Kwekkeboom DJ, Krenning EP. Peptide receptor imaging. In: Cook JR, Maisey MN, Britton KE, Chengazi V, eds. *Clinical Nuclear Medicine,* 4th edn. New York: Oxford University Press; 2006.
5. Patel YC. Somatostatin and its receptor family. *Front Neuroendocrinol* 1999; 20: 157-198.
6. Frier M. Radiopharmaceuticals. In: Cook JR, Maisey MN, Britton KE, Chengazi V, eds. *Clinical Nuclear Medicine*, 4th edn. New York: Oxford University Press; 2006.
7. Gardiner J, Langenegger D, Hoyer D et al. The enantiomer of octreotate binds to all five somatostatin receptors with almost equal micromolar affinity-a comparison with SANDOSTATIN. *Chem Biodivers* 2008; 5: 1213-1224.
8. de Jong M, Kwekkeboom DJ, Valkema R, Krenning EP. Endocrine: peptides. In: Cook JR, Maisey MN, Britton KE, Chengazi V, eds. *Clinical Nuclear Medicine,* 4th edn. New York: Oxford University Press; 2006.
9. Macke R H, Muller-Brand J.Receptor-targeted radiopeptide therapy. In: Ell JP, Gambhir SS, eds. *Nuclear Medicine in Clinical Diagnosis and Treatment*, 3rd edn. Churchill Livingstone: Elsevier Limited; 2004.
10. Wild D, Schmitt JS, Ginj M et al. DOTA-NOC, a high affiniy ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. *Eur J Nucl Med Mol Imaging* 2003; 30: 1338-1347.
11. Win Z, Rahman L, Murrell J et al. The possible role of ^{68}Ga DOTATATE PET in malignant abdominal paraganglioma. *Eur J N Med Mol Imaging* 2006; 33: 506.
12. Schonbrunn A. Somatostatin receptors: present knowledge and future directions. *Ann Oncol* 1999; 10 Suppl 2: S17-S21.
13. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumors: molecular basis for in vivo multireceptor tumor targeting. *Eur J Nucl Med Mol Imaging* 2003; 30: 781-793.
14. Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor SST1-SST5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. *Eur J Nucl Med* 2001; 28: 836-846.
15. Reubi JC, Schar JC, Waser B et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med* 2000; 27: 273-282.
16. AL-Nahhas A, Win Z, Szyszko T et al. What can gallium-68 PET add to receptor and molecular imaging? *Eur J Nucl Med Mol Imaging* 2007; 34: 1897-1901.
17. Cescato R, Schulz S, Waser B et al. Internalization of SST2, SST3, and SST5 receptors: effects of somatostatin agonists and antagonists. *J Nucl Med Med* 2006; 47: 502-511.
18. Hofmann M, Maecke H, Borner A et al. Biokinetics and imaging with the somatostatin receptor PET radioligand ^{68}Ga-DOTATOC: preliminary data. *Eur J Nucl Med* 2001; 28: 1751-1757.
19. Kowalski J, Henze M, Schuhmacher J et al. Evaluation of positron

emission tomography imaging using [^{68}Ga]-DOTA-DPhe1-Tyr^{3}-Octreotide in comparison to [^{111}In]-DTPAOC SPECT. First results in patients with neuroendocrine tumors. *Mol Imaging Biol* 2003; 5: 42-48.
20. Gabriel M, Decristoforo C, Kendler D et al. ^{68}Ga-DOTA-Tyr^{3}-Octreotide PET in Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and CT. *J Nucl Med* 2007; 48: 508-518.
21. Koukouraki S, Strauss LG, Georgoulias V et al. Evaluation of the pharmacokinetics of ^{68}Ga-DOTATOC in patients with metastatic neuroendocrine tumours scheduled for ^{90}Y-DOTATOC therapy. *Eur J Nucl Med Mol Imaging* 2006; 33: 460-466.
22. Win Z, Rahman L, Khan S et al. ^{68}Ga-DOTATATE PET imaging in neuroendocrine and neuroectodermal tumours. *Nucl Med Commun* 2006; 27: 288.
23. Win Z, Al-Nahhas A, Towey D et al. ^{68}Ga-DOTATATE PET in neuroectodermal tumours: first experience. *Nucl Med Commun* 2007; 28: 359-363.
24. Henze M, Dimitrakopoulou-Strauss A, Milker-Zabel S et al. Characterization of ^{68}Ga-DOTA-D-Phe^{1}-Tyr^{3}-octreotide kinetics in patients with meningiomas. *J Nucl Med* 2005; 46: 763-769.
25. Milker-Zabel S, Zabel-du Bois A, Henze M et al. Improved target volume definition for fractionated stereotactic radiotherapy in patients with intracranial meningiomas by correlation of CT, MRI, and [^{68}Ga]-DOTATOC-PET. *Int J Radiat Oncol Biol Phys* 2006; 65: 222-227.
26. Roivainen A, Tolvanen T, Salomaki S et al. ^{68}Ga-labeled oligonucleotides for in vivo imaging with PET. *J Nucl Med* 2004; 45: 347-355.
27. Wei L, Miao Y, Gallazzi F et al. Gallium-68-labeled DOTA-rhenium-cyclized alpha-melanocyte-stimulating hormone analog for imaging of malignant melanoma. *Nucl Med Biol* 2007; 34: 945-953.
28. Froidevaux S, Calame-Christie M, Schuhmacher J et al. A gallium-labeled DOTA-alpha-melanocyte-stimulating hormone analog for PET imaging of melanoma metastases. *J Nucl Med* 2004; 45: 116-123.
29. Reubi JC, Wenger S, Schmuckli-Maurer J et al. Bombesin receptor subtypes in human cancers: detection with the universal radioligand ^{125}I-[D-Tyr^{6},beta-Ala^{11},Phe^{13},Nle^{14}] bombesin(6-14). *Clin Cancer Res* 2002; 8: 1139-1146.
30. Zhang H, Schuhmacher J, Waser B et al. DOTA-PESIN, a DOTA-conjugated bombesin derivative designed for the imaging and targeted radionuclide treatment of bombesin receptor-positive tumours. *Eur J Nucl Med Mol Imaging* 2007; 34: 1198-1208.
31. Ito M, Yang DJ, Mawlawi O et al. PET and planar imaging of tumor hypoxia with labelled metronidazole. *Acad Radiol* 2006; 13: 598-609.
32. Sharma V, Prior JL, Belinsky MG et al. Characterization of a ^{67}Ga/^{68}Ga radiopharmaceutical for SPECT and PET of MDR1 P-glycoprotein transport activity in vivo: validation in multidrug-resistant tumors and at the blood-brain barrier. *J Nucl Med* 2005; 46: 354-364.
33. Seiz M, Dimitrakopoulou-Strauss A, Schubert GA et al. Differentiation between malignant transformation and tumour recurrence by ^{68}Ga-bombesin and ^{18}F-FDG-PET, in patients with low grade gliomas. *Hell J Nucl Med* 2008; 11: 149-152.
34. Lankinen P, Mäkinen TJ, Pöyhönen TA et al. ^{68}Ga-DOTAVAP-P1 PET imaging capable of demonstrating the phase of inflammation in healing bones and the progress of infection in osteomyelitic bones. *Eur J Nucl Med Mol Imaging* 2008; 35: 352-364.
35. Mäkinen TJ, Lankinen P, Pöyhönen T et al. Comparison of ^{18}FDG and ^{68}Ga PET imaging in the assessment of experimental osteomyelitis due to Staphylococcus aureus. *Eur J Nucl Med Mol Imaging* 2005; 32: 1259-1268.
36. Strauss LG, Dimitrakopoulou-Strauss A. The role of PET in head and neck cancer. *Hell J Nucl Med* 2008; 11: 6-11.
37. Dimitrakopoulou-Strauss A, Strauss LG. Quantitative studies using positron emission tomography (PET) for the diagnosis and therapy planning of oncological patients. *Hell J Nucl Med* 2006; 9: 10-21.