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COMMENTARY

Ga-68: A Versatile PET Imaging Radionuclide

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ABSTRACT

Gallium-68, a positron emitter, is available via $^{68}Ge/^{68}Ga$ generators. The simple chemistry and easy availability has increased its application from the clinical diagnosis to personalized therapy and has lot more potential in future.

Keywords: $^{68}Ge/^{68}Ga$ generator, Cyclotron, Bifunctional chelators, Nanoparticles.

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INTRODUCTION

The availability of ^{68}Ga as a positron emission tomography (PET) radionuclide for imaging dates back to early 60's at a time when neither PET nor fluorine-18 (F-18) was established. With the emergence of cyclotron and automated chemistry modules, F-18 radiopharmaceuticals established their empire in nuclear medicine. The resurgence of $^{68}Ge/^{68}Ga$ generator was due to the consistent efforts by radiochemists from Czechoslovakia and Russia in 20th century.[1,2] The modern $^{68}Ge/^{68}Ga$ generators have proved to be a milestone for noninvasive state-of-art PET/CT imaging. After that there was no looking back for Ga-68 imaging.

The advantages of ^{68}Ga over other PET-based radionuclides are its availability from an in-house generator independent of an onsite cyclotron. The half-life of Ga-68 is 68 minutes. Eighty-nine percent of Ga-68 decays by emitting positron of 1.92 MeV and the rest 11% by electron capture. The parent ^{68}Ge is produced in accelerator by (p, 2n) reaction on Ga_2O_3 target. ^{68}Ge decays with a half-life of 270.8 days by electron capture which enable long shelf life to generator (>6 months) and reduces the unit-dose cost. Due to short half life, Ga-68 can be eluted 2 to 3 times a day (after 3-5 hours) as per the requirement/patients number.

$^{68}Ge/^{68}Ga$ GENERATOR SYSTEM

In $^{68}Ge/^{68}Ga$ generator system, ^{68}Ge is strongly adsorbed on different solid supports such as, metal oxides (Al_2O_3, TiO_2 or SnO_2), organic (pyrogallol-formaldehyde resins) and inorganic supports (silica based).[3-6] The Ga-68 from currently available $^{68}Ge/^{68}Ga$ generators is eluted with dilute hydrochloric acid as a cationic $^{68}Ga^{3+}$. Initially the long processing was required to remove metallic impurities of solid support and Ge-68 breakthrough from Ga-68 elute. With the development of nonmetallic silica-based column, the processing step for the elution of Ga-68 was eliminated. Silica has high binding affinity for Ge which reduces the Ge-68 breakthrough to negligible level.

APPLICATION OF $^{68}Ga^{3+}$

Gallium acts as an iron analog and binds to transferrin and lactoferrin. The complex diffuses through loose endothelial junctions of capillaries at the sites of inflammation and enters the extracellular fluid. Leukocytes also migrate to sites of inflammation, degranulate and release large quantities of lactoferrin. Ga attaches to siderophores of bacteria and therefore can be used in leukopenic patients with bacterial infection and also in detecting sterile abscesses that provoke a leukocyte response.[7] In earlier times, Ga-67 citrate was very popular for infection imaging by exploiting above properties of Ga.[8] Due to low energy, long imaging time (half life: 78 hours) and poor image quality, the impact of Ga-67 imaging faded away. The resurgence of Ga-68, a PET radionuclide has revived the importance of ^{68}Ga as natural *in vivo* infection/inflammation imaging agent.[9,10] Now, the infection imaging is done using ^{68}Ga-citrate and $^{68}GaCl_3$.

$^{68}Ga^{3+}$ CHEMISTRY

^{68}Ga-complexes has simple aqueous coordinate chemistry based on Me(III).[11] Gallium, in aqueous solution, occurs solely in +3 oxidation state and is classified as a hard acid metal. Gallium can bond to highly ionic hard base ligand donors, such as carboxylic acids, amino nitrogens, hydroxamates, thiols and phenolates. The Ga chemistry is highly influenced by pH change. The optimum pH (3-5) is required for its aqueous chemistry. The pH below optimum inhibits the reaction and at pH above optimum range, i.e. >5, it tends to hydrolyze and leads to the precipitation as $Ga(OH)_3$.

Ga-68-LABELED MOLECULES

Several suitable bifunctional chelators have been developed, and coupled with biomolecules for Ga-68 labeling. DOTA, NOGADA and NOTA are commonly used bifunctional chelators. Many peptides/biomolecules like receptor

peptides and antibodies etc have now been successfully modified by these chelating agents without compromising their functional properties which further widened the role of Ga-68 PET/CT imaging. These peptides/biomolecules show very fast target localization and fast blood clearance thus, making the short half-life ideal for clinical studies. In the last decade ^{68}Ga-DOTA-octreotides replaced ^{99m}Tc/^{111}In-DTPA-octroescan used for neuroendocrine tumor (NET) imaging. ^{68}Ga-DOTA-octreotides proved to be a promising radiopharmaceutical for diagnosis, treatment planning, therapy response evaluation and disease recurrence of NET.[12] Several peptides like somatostatin for imaging NET, integrin peptide for imaging neoangiogenesis, etc. are now available as cold kits.

Ga-68 labeling has also been explored with other peptide receptors, like cholecystokinin/gastrin and GLP-1 analogs for NETs, bombesin and neuropeptide-Y analogs for prostate or breast cancers.[13-15] Arg-Gly-Asp (RGD) a cyclic tripeptide is used to image neoangiogenic/angiogenic vessels and mediated cell adhesion molecule by targeting overexpressed $\alpha_v\beta_3$ integrin. Inflammatory bowel disease, inflamed synovial tissue of rheumatoid arthritis and inflammatory atherosclerotic plaques can also be visualized by ^{68}Ga-RGD peptide.[16] Vascular adhesion protein-I (VAP 1) is an inflammation inducible endothelial cell molecule. It also contributes to extravasation cascade and controls trafficking of leukocyte at the site of inflammation. VAP-1 is expressed on the endothelial surface of intestinal blood vessels in inflammatory diseases, in skin inflammation (psoriasis), synovial blood vessels of inflamed joints (rheumatic arthritis) and cardiovascular diseases. However, VAP-1 is absent from the endothelial surface of normal tissues. Ga-68-labeled peptide against VAP-1 have been used for *in vivo* imaging of VAP-1 knockout.[17]

FUTURE

In the modern era of 'personalized medicine', Ga-68 has a promising role. The targets can be defined with the help of diagnostic Ga-68 PET/CT using appropriate ligands (peptides/biomolecules) for detection of disease, pretherapeutic measurement of organ and tumor doses. The therapeutic analog of imaging radionuclide (Lu-177/Y-90) can be selected for therapy using the same peptide. Nanomedicine in future has a great potential for early detection, accurate diagnosis and personalized treatment of various diseases, particularly cancer. Nanomedicine can offer unprecedented interactions with biomolecules, on the surface as well as inside the cells which may revolutionize disease diagnosis and treatment. Molecular imaging can measure the expression of molecular markers at different stages of diseases and provide relevant and reliable information in an intact system. The information may speed up the drug development process and help in individualized treatment monitoring and dose optimization. Ga-68 is an ideal radionuclide for labeling various nanoparticles like single-walled carbon nanotubes (SWNTs), quantum dots (QD), polymeric and metallic nanoparticles, etc. for evaluation of their biodistribution, pharmacokinetic properties and tumor targeting efficacy.[18-20] The information may be utilized for early diagnosis, selecting better treatment options and predicting the disease prognosis.

With each passing day, the reign of Ga-68 in research and clinical application is increasingly being established. It has a lot in store for future. The easy availability and simple chemistry based on sophisticated chelating agents for Ga-68 will make it parallel to kit-based Tc-99m chemistry as predicted by Deutsch.[21]

REFERENCES

1. Kopecký P, Mudrová B, Svoboda K. The study of conditions for the preparation and utilization of ^{68}Ge-^{68}Ga generator. Int J Appl Radiat Isot 1973;24:73-80.
2. Schuhmacher J, Maier-Borst W. ^{68}Ge-^{68}Ga generator for the production of ^{68}Ga in an ionic form. Int J Appl Radiat Isot 1974;25:263-68.
3. Mirzadeh S, Lambrecht R. Radiochemistry of germanium. J Radioanal Nucl Chem 1996;202:7-102.
4. Meyer GJ, Maecke H, Schuhmacher J, Knapp WH, Hofmann M. ^{68}Ga-labelled DOTA-derivatised peptide ligands. Eur J Nucl Med Mol Imag 2004;31:1097-104.
5. Velikyan I, Beyer GJ, Langstrom B. Microwave-supported preparation of ^{68}Ga bioconjugates with high specific radioactivity. Bioconjug Chem 2004;15:554-60.
6. Schuhmacher J, Maier-Borst W. A new ^{68}Ge/^{68}Ga radioisotope generator system for production of ^{68}Ga in dilute HCl. Int J Appl Radiat Isot 1981;32:31-36.
7. El-Maghraby TA. Nuclear medicine methods for evaluation of skeletal infection among other diagnostic modalities. Q J Nucl Med Mol Imaging 2006;50:167-92.
8. Palestro CJ. The current role of gallium imaging in infection. Semin Nucl Med 1994;24:128-41.
9. Mäkinen TJ, Lankinen P, Pöyhönen T, Jalava J, Aro HT, Roivainen A. Comparison of ^{18}F-FDG and ^{68}Ga PET imaging in the assessment of experimental osteomyelitis due to Staphylococcus aureus. Eur J Nucl Med Mol Imaging 2005;32:1259-68.
10. Silvola J, Laitinen I, Sipilä H, Laine VJO, Leppänen P, Ylä-Herttuala S, et al. Uptake of ^{68}gallium in atherosclerotic plaques in LDLR/ApoB100/100 mice. EJNMMI Res 2011;1:14.
11. Green MA, Welch MJ. Gallium radiopharmaceutical chemistry. Int J Rad Appl Instrum B 1989;16:435-48.
12. Naji M, AL-Nahhas A. ^{68}Ga-labelled peptides in the management of neuroectodermal tumours. Eur J Nucl Med Mol Imaging 2012;39(Suppl 1):S61-67.
13. Von Guggen Berg E, Rangger C, Sosabowski J, Laverman P, Reubi JC, Virgolini IJ, et al. Preclinical evaluation of radiolabeled DOTA-derivatized cyclic minigastrin analogs for

targeting cholecystokinin receptor expressing malignancies. Mol Imaging Biol 2012 Jun;14(3):366-75.
14. Brom M, Oyen WJG, Joosten L, Gotthardt M, Boerman OC. Ga-labelled exendin-3, a new agent for the detection of insulinomas with PET. Eur J Nucl Med Mol Imaging 2010; 37:1345-55.
15. Schuhmacher J, Zhang H, Doll J, Mäcke HR, Matys R, Hauser H, et al. GRP receptor-targeted PET of a rat pancreas carcinoma xenograft in nude mice with a 68Ga-labeled bombesin (6-14) analog. J Nucl Med 2005;46:691-99.
16. Knetsch PA, Petrik M, Griessinger CM, Rangger C, Fani M, Kesenheimer C, et al. [68Ga]NODAGA-RGD for imaging $\alpha_v\beta_3$ integrin expression. Eur J Nucl Med Mol Imaging 2011;38: 1303-12.
17. Autio A, Ujula T, Luoto P, Salomäki S, Jalkanen S, Roivainen A. PET imaging of inflammation and adenocarcinoma xenografts using vascular adhesion protein 1 targeting peptide (68)Ga-DOTAVAP-P1: Comparison with (18)F-FDG. Eur J Nucl Med Mol Imag 2010;37:1918-25.
18. Liu Z, Cai W, He L, Nakayama N, Chen K, Sun X, et al. In vivo biodistribution and highly efficient tumor targeting of carbon nanotubes in mice. Nat Nanotechnol 2007;2:47.
19. Cai W, Chen K, Li ZB, Gambhir SS, Chen X. Dual-function probe for PET and near-infrared fluorescence imaging of tumor vasculature. J Nucl Med 2007;48:1862-70.
20. Lee HY, Li Z, Chen K, Hsu AR, Xu C, Xie J, et al. PET/MRI dual-modality tumor imaging using arginine-glycine-aspartic (RGD)–conjugated radiolabeled iron oxide nanoparticles. J Nucl Med 2008;49:1371-79.
21. Deutsch E. Clinical PET: Its time has come? J Nucl Med 1993; 34:1132-33.

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