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Review

Clinical applications of Gallium-68

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HIGHLIGHTS

- A summary of the emerging clinical uses of ^{68}Ga-based radiopharmaceuticals is provided.
- ^{68}Ga-PET may prove as or more clinically robust than the corresponding ^{18}F-labeled agents.
- ^{68}Ga-radiopeptides were studied for targeting of somatostatin receptors subtypes.
- ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC, are currently in clinical trials.

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ABSTRACT

Gallium-68 is a positron-emitting radioisotope that is produced from a ^{68}Ge/^{68}Ga generator. As such it is conveniently used, decoupling radiopharmacies from the need for a cyclotron on site. Gallium-68-labeled peptides have been recognized as a new class of radiopharmaceuticals showing fast target localization and blood clearance. ^{68}Ga-DOTATOC, ^{8}Ga-DOTATATE, ^{68}Ga-DOTANOC, are the most prominent radiopharmaceuticals currently in use for imaging and differentiating lesions of various somatostatin receptor subtypes, overexpressed in many neuroendocrine tumors. There has been a tremendous increase in the number of clinical studies with ^{68}Ga over the past few years around the world, including within the United States. An estimated ~10,000 scans are being performed yearly in Europe at about 100 centers utilizing ^{68}Ga-labeled somatostatin analogs within clinical trials. Two academic sites within the US have also begun to undertake human studies. This review will focus on the clinical experience of selected, well-established and recently applied ^{68}Ga-labeled imaging agents used in nuclear medicine.

Contents

1. Introduction

Gallium-68 is one of the earliest of the positron-emitting radionuclides to have been applied to clinical medicine, dating back to the

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early 1960s (Anger and Gottschalk, 1963), long before [^{18}F]-fluorodeoxyglucose (FDG) (Ido T et al., 1978). Because of concurrent advances in positron emission tomography (PET) and radiosynthetic accessibility of ^{68}Ga-labeled agents using standard methods of the day, Gottschalk et al., 1966 began to apply ^{68}Ga clinically, initially to central nervous system processes (Anger and Gottschalk, 1963; Schaer et al., 1966). By the late 1970s, however, ^{68}Ga-based PET imaging was sidetracked in favor of new agents coming online that utilized ^{99m}Tc for single photon emission computed tomography (SPECT) and ^{18}F for PET. One reason for this temporary delay in the development of ^{68}Ga-PET could have been because early ^{68}Ga-generators provided ^{68}Ga in complex with ethylenediaminetetraacetic acid (EDTA) such that destruction of the complex was necessary for preparation of the radiopharmaceuticals. That made radiolabeling tedious, time-consuming, and accomplished with overall poor yield. At that time ^{68}Ga-generators utilized ^{68}Ga(III) in hydrated form until next-generation ^{68}Ge/^{68}Ga generators became commercially available, which enabled convenient elution of cationic ^{68}Ga with dilute acid (0.1 M HCl). The development of these generators was recently reviewed in detail by Maecke et al. (Fani et al., 2008). Asti et al. (Asti et al., 2008) described an effective purification of the ^{68}Ge/^{68}Ga eluate [a crucial labeling step (Zhernosekov et al., 2007)], which was applied to the production of ^{68}Ga-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid–D-Phe^1-Tyr^3-octreotide, (^{68}Ga-DOTATOC), the most widely used ^{68}Ga-based PET radiopharmaceutical (Prata, 2012). This purification technique has also been used to optimize ^{68}Ga-labeling methods for DOTA-derivatized peptides and is suitable for clinical use. Decristoforo et al. described a fully automated synthesis for ^{68}Ga-labeled peptides with high, reproducible yields (Decristoforo et al., 2007). Currently several ^{68}Ge/^{68}Ga generator systems are commercially available from distributors in Russia, Europe, United States and other countries. With the availability and reliability of commercial generator systems and effective and convenient purification steps, ^{68}Ga has the potential to become as useful for PET as ^{99m}Tc has proved for SPECT imaging. There are many examples of the use of ^{68}Ga-labeled radiotracers, including many that currently rely on ^{99m}Tc clinically, such as for myocardial perfusion and function, blood flow, renal function and liver function (Baum and Rosch, 2011; Fani et al., 2008; Roesch and Riss, 2010; Rosch and Baum, 2011; Wadas et al., 2010). ^{68}Ga-based radiopeptides have been tested pre-clinically for the targeting of somatostatin (Froidevaux et al., 1999), bombesin (Schuhmacher et al., 2005b) and melanocortin 1 receptors (Froidevaux et al., 2004). Because their pharmacokinetics are well-matched to the short physical half-life of the isotope, ^{68}Ga-based peptides are increasingly recognized as a new class of radiopharmaceuticals, showing very fast blood clearance and fast target localization. The short physical half-life of ^{68}Ga ($t_{1/2}$=68 min) enables improved dosimetry and repeat imaging, making these agents ideal for clinical use. However, although of demonstrated utility in pre-clinical and limited clinical studies, no ^{68}Ga-labeled pharmaceutical has been approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) and no FDA- or EMA-approved ^{68}Ge/^{68}Ga generator is available as of this writing (Ambrosini et al., 2011a). There are two sites in the US that are currently implementing ^{68}Ga-DOTATOC, one at Vanderbilt University, under an Investigational New Drug application, where a Phase I trial has recently been completed, and the other at the University of Iowa, under approval by the local Radioactive Drug Research Committee (Graham and Menda, 2011).

2. ^{68}Ga-Labeled PET radiopharmaceuticals

There are many practical and economic advantages to ^{68}Ga. Gallium-68 is a generator-eluted, short-lived radionuclide decaying 89% through positron emission (maximum energy of 1.92 MeV, mean 0.89 MeV). The long physical $t_{1/2}$ of the parent radionuclide (270.8 d) allows the use of the generator for up to one year, obviating the need for a cyclotron on site, providing cost-effectiveness as well as convenience. However, energy of the emitted positron from ^{68}Ga is higher than that of ^{18}F (maximum energy=0.63 MeV, mean-=0.25 MeV), the most widely used PET isotope, which can potentially lead to lower resolution (Sanchez-Crespo et al., 2004). Despite the availability of ^{68}Ga for more than 30 years, recognition of its uses for clinical PET are only now emerging and only now is it being applied to pre-clinical models of human disease (Banerjee et al., 2010). Radiometals for the clinic can be used as the chelated metal itself ["metal essential radiopharmaceutical," following the definition of Jurrison et al. for ^{99m}Tc-based radiopharmaceuticals (Jurisson and Lydon, 1999)], the pharmacokinetics of which rely entirely on the physical and chemical properties of the agent, e.g. ^{68}Ga-EDTA and ^{68}Ga-diethylene triamine pentaacetic acid (^{68}Ga-DTPA). Similarly, "target-specific gallium radiopharmaceuticals" can be defined as a class of radiopharmaceuticals for which the targeting moiety (e.g., antibody, peptide, hormone) has been radiolabeled with ^{68}Ga and can be targeted to a specific, biologically accessible protein such as a receptor. In the case of ^{68}Ga the most prevalent such compounds to date target the somatostatin receptor (SSTR). Target-specific ^{68}Ga-based agents are mostly generated using a bifunctional chelating approach (BFCA). This approach requires the chelator to bind the metal in complex on one end with high affinity, enabling stability in vivo, with a targeting or affinity agent on the other end that assures concentration in the tissue of interest. Several suitable bifunctional chelators have been developed for complexation of ^{68}Ga and have been coupled to biologically active targeting agents. These include agents that contain 1,4,7-triazacyclononane-N,N′,N″-triacetic acid (NOTA), DOTA, DTPA and desferrioxamine B (DFO). Although not used in clinical trials to date, mono- and multimeric phosphinic acid derivatives of NOTA, a new class of NOTA-based chelating agents developed by Notni et al., are receiving considerable attention (Notni et al., 2010, 2012a, 2012b; Simecek et al., 2012a, 2012b). The novel bifunctional triazacyclononane triphosphinic acid chelator (TRAP) ligands have many desirable properties required for a chelating agent for ^{68}Ga, including fast and selective complex formation, high complex stability, ability to be conjugated and convenient synthesis (Notni et al., 2010, 2012a, 2012b; Simecek et al., 2012a, 2012b). The TRAP-peptide could be radiolabeled with ^{68}Ga excellent reproducibility and >95% radiochemical yield in specific activities of 10 to 20 times higher than NOTA and DOTA peptides, respectively (Notni et al., 2012b).

Targeting agents are coupled *via* the BFCA leveraging standard intermediates that enable covalent attachment including active esters, isothiocyanates, maleimides, hydrazides, or haloamides (Liu and Edwards, 1999). DOTATOC (Hofmann et al., 2001; Kowalski et al., 2003), DOTA–D-Phe^1-Tyr^3-Thr^8-octreotate (^{68}Ga-DOTATATE) (Antunes et al., 2007; Reubi et al., 2000a), ^{68}Ga-DOTA-Phe^1-Nal^3-octreotide (DOTANOC) (Wild et al., 2005, 2003), ^{68}Ga-DOTA-bombesin (Schuhmacher et al., 2005b), ^{68}Ga-NOTA-RGD (Jeong et al., 2008), ^{68}Ga-DOTA-albumin (Hoffend et al., 2005; Mier et al., 2005), ^{68}Ga-DOTA-human epidermal growth factor (hEGF) (Baum et al., 2010), ^{68}Ga-phosphonate triazacyclononane [NOPO)]–RGDfK and [^{68}Ga]-NOPO–NOC(Simecek et al., 2012b), are examples of such agents. Recently, a smart strategy employing copper-free click chemistry has been reported for site-specific coupling of bioactive molecules with chelating agents for radiolabeling with ^{68}Ga (Baumhover et al., 2011; Schultz et al., 2010). Fast and efficient coupling has been possible using an azide-modified bioactive function and a reactive cyclooctyne group attached to a chelating agent such as DOTA and NOTA.

With that background in mind, this review will focus strictly on clinical application of ^{68}Ga-based radiopharmaceuticals. Excellent recent and general reviews on the development of