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Experience in production of ^{68}Ga-DOTA-NOC for clinical use under an Expanded Access IND

Mark A. Green*, Carla J. Mathias, James W. Fletcher

Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, 46202 United States

HIGHLIGHTS

- [^{68}Ga]Ga-DOTA-NOC was produced for clinical use under the Expanded Access IND mechanism.
- Start-up and operating costs were minimized via a manual approach to synthesis.
- The ITG and Eckert & Ziegler ^{68}Ga-generators both provided acceptable performance.
- Radiopharmaceutical synthesis did not require pre-purification of the generator eluate.
- [^{68}Ga]Ga-DOTA-NOC was reliably provided at high radiochemical purity (99.2 ± 0.4%).

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ABSTRACT

[^{68}Ga]Ga-DOTA-NOC was produced under an Expanded Access IND for 174 clinical PET/CT studies to evaluate patients with neuroendocrine tumors. Production employed either the TiO_2-based Eckert & Ziegler (EZAG) ^{68}Ge/^{68}Ga-generator (with fractionated elution), or the SiO_2-based ITG ^{68}Ge/^{68}Ga-generator. In both cases, [^{68}Ga]Ga-DOTA-NOC was reliably produced, *without pre-synthesis purification of the* ^{68}Ga *generator eluate*, using readily-implemented manual synthesis procedures. [^{68}Ga]Ga-DOTA-NOC radiochemical purity averaged 99.2 ± 0.4%. Administered ^{68}Ga dose averaged 181 ± 22 MBq, and administered peptide mass averaged 43.2 ± 5.2 μg (n=47) and 23.9 ± 5.7 μg (n=127), respectively, using the EZAG and ITG generators. At dose expiration, ^{68}Ge breakthrough in the final product averaged 2.7×10^{-7}% and 5.4×10^{-5}% using the EZAG and ITG generators, respectively.

1. Introduction

Gallium-68-labeled somatostatin-receptor-targeted peptides, such as [^{68}Ga]Ga-DOTA-NOC, [^{68}Ga]Ga-DOTA-TOC, and [^{68}Ga]Ga-DOTA-TATE, have found widespread clinical use in Europe for positron emission tomography (PET) detection of neuroendocrine tumors (Virgolini et al., 2010; Pettinato et al., 2008; Prasad and Baum, 2010; Prasad et al., 2010; Ambrosini, 2010), but none are FDA-approved drug products in the USA. These three targeting peptides vary slightly in amino acid sequence, resulting in variations in their receptor affinities and receptor-sub-type selectivity (Antunes et al., 2007), but all appear suitable for use in clinical imaging (Virgolini et al., 2010).

The Expanded Access IND (Investigational New Drug exemption) can be a mechanism for providing patient access to a drug product that is not FDA-approved, but that is clinically needed in treatment of a serious disease (21CFR312.305, 2013). In response to a local clinical need to better define the location and extent of disease in neuroendocrine cancer patients who are candidates for multivisceral transplant (Mangus et al., 2013), a manual synthesis method was developed for on-demand preparation of the [^{68}Ga]Ga-DOTA-NOC peptide-chelate conjugate in a formulation suitable for intravenous administration, and an Expanded Access IND submitted to the FDA documenting the production procedure and the intended clinical use. We selected [^{68}Ga]Ga-DOTA-NOC because our clinical focus was to define extent of disease, and this agent offers affinity for a broader range of receptor sub-types than [^{68}Ga]Ga-DOTA-TOC or [^{68}Ga]Ga-DOTA-TATE ([^{68}Ga]Ga-DOTA-NOC exhibits significant affinity for ssrt3, sstr4, sstr5, as well as the sstr2 receptor sub-type most commonly expressed by neuroendocrine tumors) (Antunes et al., 2007).

We describe here our experience with manual radiochemical synthesis of [^{68}Ga]Ga-DOTA-NOC for clinical use under Expanded Access IND 117,255. The manual approach to synthesis was chosen because of the expected limited production volume, and the desire

* Correspondence to: Department of Radiology, Indiana University School of Medicine, 950 W. Walnut St.; R2 – E124, Indianapolis, IN 46202, United States.
E-mail address: magreen@iu.edu (M.A. Green).

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for a simple process that could be rapidly implemented and validated with minimal expense, since start-up and dose production costs needed to be recovered by charges to the patient.

2. Materials and methods

As required for an Expanded Access IND by the U. S. Food and Drug Administration (FDA), our clinical use of [^{68}Ga]Ga-DOTA-NOC in clinical PET/CT imaging was reviewed and approved by an Indiana University Institutional Review Board (IRB). All patients provided written informed consent prior to administration of the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical. Clinical imaging was generally performed as an outpatient procedure using a Siemens mCT extended FOV time-of-flight PET/CT (128 slice) camera, with a few in-patient studies instead performed using a Siemens Biograph-64 PET/CT. Whole-body (head to mid-thigh) PET acquisitions were started at 60-min post-injection with data collection occurring over a period of ~24-min.

The DOTA-NOC peptide conjugate was purchased from ABX GmbH as commercial cGMP-grade product packaged at 60-μg per vial. Two TiO_2-based Eckert & Ziegler (EZAG) IGG100 ^{68}Ge/^{68}Ga generators (50-mCi; 1.85 GBq), and four SiO_2-based ITG Isotope Technologies Garching GmbH ^{68}Ge/^{68}Ga generators (30-mCi; 1.11 GBq), have been employed to supply ^{68}Ga for manual synthesis of [^{68}Ga]Ga-DOTA-NOC under Expanded Access IND #117,255. While not specified by the generator manufacturers, in both cases we filtered the aqueous HCl generator eluent through an HCl-stable 25-mm sterile 0.2-μm filter (Supor® polyethersulfone membrane in acrylic housing, part #H938210023, Baxa, Englewood, CO) attached to the generator inlet. To minimize introduction of trace metal impurites that would compete with $^{68}Ga^{3+}$ for binding the DOTA-NOC chelator, generator eluent was prepared by dilution of ultrapure concentrated HCl (HCl 30%, Suprapur®, EM Science, Gibbstown, NJ) with ultrapure water (NERL®, Thermo Scientific, Middletown, VA). Reaction mixture buffering employed only ultrapure sodium acetate (99.999%; Atomergic Chemetals Corporation, Farmingdale, NY) in a 0.25 M solution prepared using ultrapure water.

Synthesis of the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical employed no-carrier-added $^{68}Ga^{3+}$ in either 1.5 mL 0.1 M ultrapure HCl (fractionated elution of the EZAG generator), or 4.0-mL 0.05 M ultrapure HCl (ITG generator, without fractionation). The eluate was buffered to pH ~4.8 by addition of ultrapure NaOAc and reacted with the DOTA-NOC conjugate (60-μg for the EZAG eluate; 30-μg for the ITG eluate) with heating for 10-min. For our initial manual synthesis method, the reaction mixture was heated in a sterile 15-mL polypropylene centrifuge tube using an Eppendorf Thermomixer (Fig. 1) set at 80 °C. Using the ITG generator we initially employed this same synthetic method, but then adapted our process to employ ITG's manually controlled Fluidic Module (Vis et al., 2015; Tworowska et al., 2016; Roesch, 2012) for better radiation shielding during solution transfers. Required solution transfers in our process using the EZAG generator were simply made using syringes and needles (4-inch B Braun Medication Transfer Filter Straws and 3.5-inch 18-gauge spinal needles), employing tungsten syringe shields to minimize hand exposure. The ITG Fluidic Module (Vis et al., 2015; Tworowska et al., 2016; Roesch, 2012) employs a single-use assembly of a reaction vessel that is plumbed with sterile medical tubing and Luer adapters, connectors, and valves; the radiochemical synthesis can then proceed in a compact shielded bench-top unit using external syringes for reagent additions and transfers, with the operator manually controlling fluid pathways via external knobs for changing the positions of the enclosed 3-way and 2-way valves. Following ITG's recommended protocol, the thermostat for the Fluidic Module heating element was set to 105 °C, resulting in a reactor solution temperature of 90–100 °C.

Fig. 1. Eppendorf Thermomixer fitted with the heating element for a 15-mL centrifuge tube. In our initial manual synthesis method, a single-use sterile centrifuge tube containing the [^{68}Ga]Ga-DOTA-NOC reaction solution was simply heated in the 80 °C thermomixer with swirling at ≥300 rpm for 10-min to complete the labeling reaction (with the apparatus shielded within >5-cm walls of lead bricks).

The [^{68}Ga]Ga-DOTA-NOC product was always isolated by C18 solid-phase extraction (Waters C18 SepPak® Light), and then washed by passage of 5–10 mL of either sterile water or sodium chloride for injection. (Prior to use, the C18 solid phase extraction cartridge was conditioned by flushing with 5–10 mL absolute ethanol USP, followed by 10-mL sterile water for injection.) To reliably maintain trapping efficiency for the [^{68}Ga]Ga-DOTA-NOC product, loading to the C18 solid-phase extraction cartridge needed to occur very slowly (*i.e.*, with drop-wise flow at the outlet) if the reaction mixture was transferred without prior cooling.

The [^{68}Ga]Ga-DOTA-NOC was then recovered by elution of the C18 SepPak® with ethanol: saline (0.6-mL, 85:15; or 1.0-mL, 50:50), collecting the intermediate product in a sterile polypropylene centrifuge tube where it was diluted to ≤5% ethanol with either 12-mL or 10-mL sterile saline. The [^{68}Ga]Ga-DOTA-NOC intermediate product solution was then drawn into a shielded sterile syringe for terminal sterilizing filtration (13-mm 0.2-μm PVDF filter, Whatman™ 6791–1302, GE Healthcare Life Sciences) within a laminar flow hood into a sterile evacuated vial (30-mL, vial #7521ZA, Jubilant HollisterStier, Spokane, WA; Fig. 2). Since the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical was always being prepared for immediate use, the dose expiration time was set as 60-min after the sterilizing filtration to yield final product.

Pre-release product quality control procedures included: half-life measurement for confirmation of radionuclidic identity; pH measurement; ITLC assessment of radiochemical purity; endotoxin testing (Endosafe®-PTS, Charles River Laboratories); and a bubble point measurement to confirm the integrity of the single-use sterile 0.2-μm filter employed for terminal product sterilization. The half-life determination was made using a radionuclide dose

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