

Automated Preparation of [⁶⁸Ga]DOTATOC for Imaging Neuroendocrine Tumor Patients at the University of Iowa: Initial Experiences

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Abstract

Objectives. Gallium-68 (⁶⁸Ga) somatostatin analogs are the gold standard for PET imaging of neuroendocrine tumors, yet have not been embraced in the United States. In this study, an automated system for preparation of [⁶⁸Ga]DOTATOC is evaluated based on system performance and quality control parameters. The system was used to prepare patient doses for biodistribution research studies in human subjects and results compared to Octreoscan™ SPECT.

Methods. The automated system (ModularLab PharmTracer, Eckert-Ziegler, Berlin, Germany) combines a titanium dioxide based germanium-68 (⁶⁸Ge)/⁶⁸Ga generator (IGG100 Eckert-Ziegler) with a computer-controlled system that employs complete, single-use, sterile, GMP-grade, cassettes. In this study, 1.85 GBq ⁶⁸Ga was eluted (6 mL 0.1 M hydrochloric acid, HCl) to an in-line cation exchange resin, which retains ⁶⁸Ga. Purified ⁶⁸Ga is eluted with 98% acetone/0.02 M HCl to a glass reaction vessel containing 30 µg DOTATOC (in 2 mL acetate buffer, pH 4). Radiolabeling is carried out at 95°C for 6 min. Acetone is removed by vent to waste. [⁶⁸Ga]DOTATOC is then transferred to an in-line C-18 cartridge. Free ⁶⁸Ga is removed by saline rinse and pure [⁶⁸Ga] DOTATOC is eluted in 1:1 95% ethanol:water to the product vial through a sterilizing filter (and diluted with saline). QC parameters were measured by standard techniques.

Results. Sterile, pyrogen-free [⁶⁸Ga]DOTATOC was prepared in 32 min. Reagent preparation and system setup requires about 30 minutes of technician effort. QC metrics were acceptable: specific activity > 25 MBq nmole⁻¹, radiochemical purity >98%; pH 6; acetone, ethanol, and pyrogen levels within limits. Excellent tumor contrast was observed in these initial biodistribution studies in human subjects.

Conclusions. The automated system enabled rapid [⁶⁸Ga]DOTATOC preparations with quality control parameters within acceptable limits for biodistribution studies in humans. Initial studies in human subjects displayed excellent tumor contrast and favorable pharmacodynamics. The system and integrated software can be adapted readily for training of personnel and daily operations.

Background and Objectives

Neuroendocrine tumors (NET) comprise a family of enigmatic malignancies whose incidence has increased 5-fold over the past three decades.^{1,2} Despite advances in overall cancer related mortality, most patients with NETs are not diagnosed until liver metastases have developed, at which time <30% survive 5 years.³ Improved methods for diagnosing, treating, and monitoring response to therapy are critically needed for these patients. Our laboratories are exploring peptide-based targeted radionuclide imaging and therapy of NET as promising avenues for adult and pediatric NET patients.³⁻⁷ For imaging, indium-111 (¹¹¹In) labeled DTPA-Octreotide (Octreoscan™) scintigraphy, has been the standard of care in the United States. However, Octreoscan images have low resolution and are not quantitative. On the other hand, [⁶⁸Ga]DOTATOC imaging of NET by PET has demonstrated promise as a molecular imaging tool for diagnosing and monitoring of NET,⁸⁻¹⁰ but has not been adopted widely in the United States.

In this study, we describe our first experiences with preparation of [⁶⁸Ga]DOTATOC using a classical ⁶⁸Ge/⁶⁸Ga generator combined with an automated cassette-based modular radiolabeling and purification system (ModularLab PharmTracer) for dose preparation that includes hardware and computer software graphical user interface for automated operation. The system was evaluated for quality control parameter performance measures. Based on successful performance of the system, biodistribution studies in human subjects were performed.

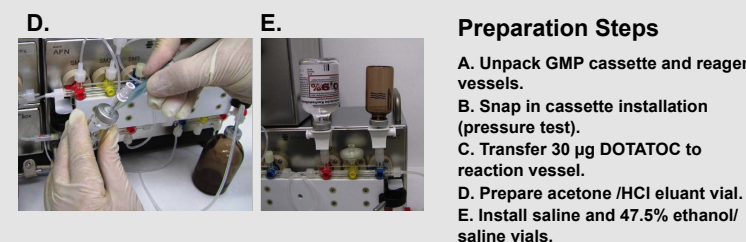
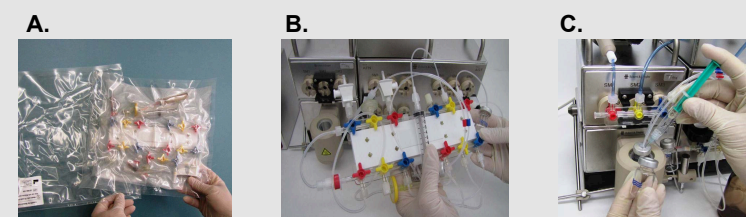
In vivo Imaging Studies

The ongoing study is open to adult subjects with biopsy proven, metastatic neuroendocrine tumor and is performed under local Radiation Drug Research Committee (RDRC) approval to evaluate the biodistribution and reproducibility of [⁶⁸Ga]DOTATOC PET uptake measurements in normal organs and tumor tissue. Subjects must be 18 years or older; histological diagnosis of neuroendocrine tumor and have at least one lesion identified on conventional imaging.

PET imaging included dynamic PET images of the chest or abdomen over 60 min followed by whole body PET-CT images from the top of the head to proximal thighs. An example comparison of [⁶⁸Ga]DOTATOC and Octreoscan SPECT is shown in results presented here.

Operation and Quality Control

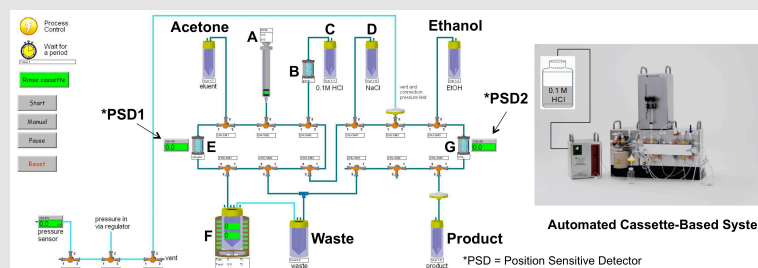
Reagent Preparations and System Pre-Run QC (30 min)



Preparation Steps

- Unpack GMP cassette and reagent vessels.
- Snap in cassette installation (pressure test).
- Transfer 30 µg DOTATOC to reaction vessel.
- Prepare acetone /HCl eluant vial.
- Install saline and 47.5% ethanol/ saline vials.

Software Operation for [⁶⁸Ga]DOTATOC Preparation (32 min)



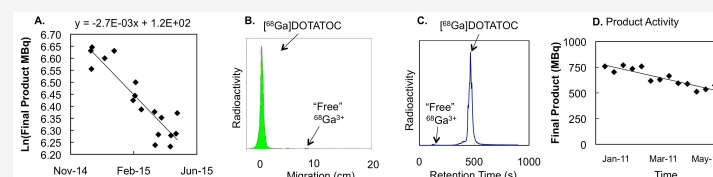
Operation: The system is operated using remote-automated software installed on a laptop computer. A cassette pressure test is run initially to test the integrity of the connections and valves (2 min.). A C-18 cartridge (G) is re-rinsed with ethanol and saline (D). A syringe mounted pump (A) draws ⁶⁸Ga from the generator (B) using 6 mL 0.1 M HCl (C). The solution is passed through a cation exchange resin bed (E), which retains ⁶⁸Ga. Purified ⁶⁸Ga is eluted from the cation exchange column in 1 mL of 98% acetone/0.02 M HCl to the reaction vessel that is housed by the heating module (F), which contains a solution of 30 µg DOTATOC in 2 mL pH 4 acetate buffer. The solution is heated to 100 °C for 6 minutes, cooled with 2 mL saline (D) and transferred to a C-18 cartridge (G), which retains [⁶⁸Ga]DOTATOC. Free ⁶⁸Ga is rinsed from the C-18 cartridge with saline (D) and the final product is eluted in 1 mL 47.5% ethanol and diluted to ~7 mL saline before transfer via sterilizing filter to the final product vial (32.5 minutes).

Results

Quality Control

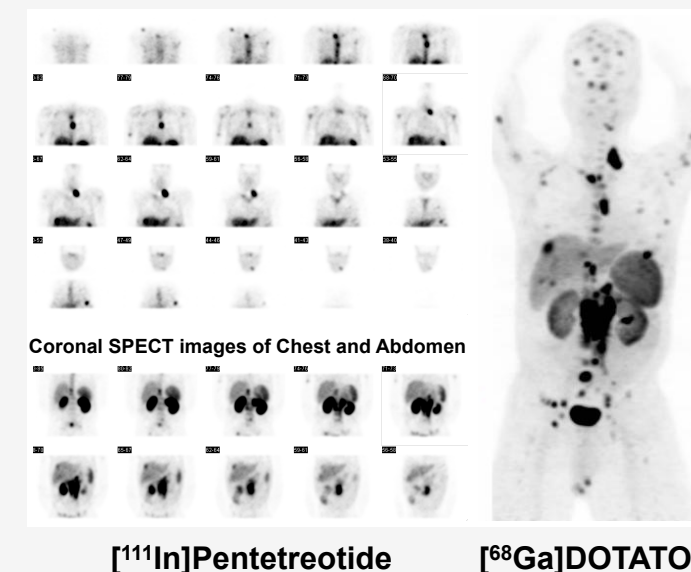
Table 1. Quality performance testing of [⁶⁸Ga]DOTATOC prepared using the automated cassette-based system (n=12)

Parameter	Test Method	Specification	Result ± SD	% Pass
Radiochemical Purity (%)	ITLC*	> 90%	98±1	100
Specific Activity (MBq nmole ⁻¹)	Dose Calibrator	20 MBq nmole ⁻¹	31±4	100
Acetone	Gas Chromatography	< 5000 ppm ^a	399±64	100
Ethanol	Gas Chromatography	< 10%	5±0	100
Endotoxins	Limulus Amebocyte Lysate	< 175 EU ^b mL ⁻¹	25±0	100
Sterility	Fluid Thioglycolate Soybean Casein	No Turbidity 14 days	Pass	100
pH	pH paper	4.5-8.5	6±1	100
Filter Pressure Test	Automated N ₂ Stream	2 bar	Pass	100



⁶⁸Ga generator performance. These data show that the cassette-based system is stable and provides high radiochemical purity [⁶⁸Ga]DOTATOC. Methods: (A) Plot of the natural log [⁶⁸Ga]DOTATOC dose vial radioactivity (MBq) per run over time. Slope of linear fit gives a calculated half life of 255 days (94% of known) demonstrating generator is stable to ⁶⁸Ge breakthrough; (B) Instant thin layer chromatography method developed to enable determination of the radiochemical purity within 10 minutes (2.5 min migration time and 5 minutes counting) for rapid dose delivery; and (C) Confirmation of the iTLC radiochemical purity by radioHPLC; (D) Final product activity over the study period.

Octreoscan and Ga-68 DOTATOC PET



55 y/o male with widely metastatic carcinoid tumor. Symptoms include diarrhea and flushing with chromogranin level 6700.

Note substantially larger number of disease sites depicted on PET image compared to SPECT.

Conclusions

The automated ModularLab PharmTracer system enabled rapid [⁶⁸Ga]DOTATOC preparations with quality control parameters within acceptable limits for biodistribution studies in humans. The system and integrated software can be adapted readily for training of personnel and daily operations.

References and Support

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