Automated Preparation of $^{68}$GaDOTATOC for Imaging Neuroendocrine Tumor Patients at the University of Iowa: Initial Experiences


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Abstract

Objective: Gallium-68 ($^{68}$Ga) 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 $^{68}$GaDOTATOC 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 Octroscan $^{111}$SPECT.

Methods: The automated system (ModularLab PharmTracer; Eckerti-Ziegler, Berlin, Germany) combines a titanium dioxide based germanium-68 ($^{68}$Ge/$^{68}$Ga) generator (IGG100 Eckerti-Ziegler) with a computer-controlled system that employs complete, single-use, sterile, GMP-grade, capsules. In this study, 1.85 GBq ($^{68}$Ga) was studied (6 mL, 0.1 M hydrochloric acid, HCI) to an in-line cation exchange resin, which retains $^{68}$Ga. Purified $^{68}$Ga is eluted with 0.02 M HCI to a glass reaction vessel containing 30 µg DOTATOC (in 2 mL, acetate buffer, pH 4). Radioactivity is carried out at 95°C for 6 min. Acetone is removed by vent in line. $^{68}$GaDOTATOC is then transferred to an in-line C-18 cartridge. Free $^{68}$Ga is removed by saline rinse and pure $^{68}$Ga DOTATOC is eluted in 1:1 95% ethanol:water to the product vial through a sterilizing filter (and diluted with saline). QC parameters were evaluated for quality control parameter performance measures. The system was used to prepare patient doses for biodistribution research studies in normal organs and tumor tissues. 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 $^{68}$GaDOTATOC and Octroscan SPECT is shown in results presented here.

Results

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

A. Reagent prepreparations with quality control parameter evaluation for biodistribution studies in humans. Initial studies in human subjects displayed excellent tumor contrast and favorable pharmacokinetics. 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. Despite advances in overall cancer related mortality, most patients with NETs are not diagnosed until liver metastases have developed, at which time <35%, survive 5 years. 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. For imaging, indium-111 ($^{111}$In) labeled DOTA-Tyr3-Octreotide (Octreoscan®) scintigraphy, has been the standard of care in the United States. However, Octroscan images have low resolution and are not quantitative. On the other hand, $^{68}$GaDOTATOC imaging of NET by PET has demonstrated promise as a molecular imaging tool for diagnosing and monitoring of NET, but has not been adopted widely in the United States.

In this study, we describe our first experiences with preparation of $^{68}$GaDOTATOC using a classical $^{68}$Ge/$^{68}$Ga 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 biodistribution and 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 $^{68}$GaDOTATOC. PET uptake measurements in normal organs and tumor tissues. 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 $^{68}$GaDOTATOC and Octroscan SPECT is shown in results presented here.

Quality Control

Table 1. Quality performance testing of $^{68}$GaDOTATOC prepared using the automated cassette-based system (n=12)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Method</th>
<th>Specification</th>
<th>Result ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiolabeling purity (%)</td>
<td>TLC</td>
<td>&gt; 95%</td>
<td>98±1</td>
</tr>
<tr>
<td>Specific activity (MBq/µg)</td>
<td>Sieve Cellulose</td>
<td>&lt; 500 ppm</td>
<td>134±3</td>
</tr>
<tr>
<td>Acetone Ge Chromatography</td>
<td>80%</td>
<td>89±9±4</td>
<td></td>
</tr>
<tr>
<td>Ethanol Ge Chromatography</td>
<td>&lt; 10%</td>
<td>5±f</td>
<td></td>
</tr>
<tr>
<td>Chromatography</td>
<td>Column</td>
<td>173±5, 4 mL</td>
<td>255±4</td>
</tr>
<tr>
<td>Radiochemical Purity (%)</td>
<td>C18 cartridge</td>
<td>&gt; 90%</td>
<td>100</td>
</tr>
<tr>
<td>Filter Pressure Test</td>
<td>Automated N. Stream</td>
<td>1 µm Pass</td>
<td>100</td>
</tr>
</tbody>
</table>

For $^{68}$Ga generator performance. These data show that the cassette-based system in stable and provides high radiochemical purity ($^{68}$GaDOTATOC). Methods: (A) Plot of the natural log ($^{68}$GaDOTATOC) dose vs radioactivity (MBq) per run over time. Slope of linear fit gives a calculated half life of 205 days (94% of known) demonstrating generator is stable to $^{68}$Ga. (B) C18 transient chromatography (2 mL, 300 µL fraction, 0.2 mL/min, 25°C) to chromatograph $^{68}$GaDOTATOC within acceptable limits for biodistribution studies in humans. The system and integrated software can be adapted readily for training of personnel and daily operations.

Conclusions

The automated ModularLab PharmTracer system enabled rapid $^{68}$GaDOTATOC 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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