Dosimetry and Biodistribution of an Iodine-123-Labeled Somatostatin Analog in Patients with Neuroendocrine Tumors


Departments of Radiology, Oncology and Radiation Safety, Mayo Clinic, Rochester, Minnesota

A modified method for the preparation of a radiolabeled analog of somatostatin (\(^{123}\)I-octreotide) is described. The pharmacokinetics and dosimetry of this analog were evaluated in patients with neuroendocrine tumors. Thirty patients had multiple blood and urine samples and sequential anterior and posterior whole-body scintigraphy up to 40 hr postinjection of \(^{123}\)I-octreotide. Region of interest analysis of the whole-body images was used to determine organ and tumor doses. The \(^{123}\)I-octreotide was rapidly cleared from the blood with a \(T_{1/2}\) of 10 min by the hepatobiliary system. By 40 hr, approximately 55% was eliminated in the feces. The gallbladder wall received the highest dose (0.48 rad/mCi), with other organs receiving doses of 0.12 rad/mCi or less. Tumors were identified in 25 of 28 satisfactory studies. Tumor doses ranged from 0.1 to 0.6 rad/mCi, while average tumor doses would range from 0.9 to 5.0 rad/mCi. Iodine-123-octreotide is a useful agent for the visualization of neuroendocrine tumors. The rapid washout of this agent from tumors precludes the possibility of radiotherapy with \(^{123}\)I-octreotide in these patients.

**PATIENTS AND METHODS**

Patients

A total of 30 patients were studied (12 male, 18 female) with an average age of 52 ± 14 yr. All patients had a histologically or cytologically confirmed diagnosis of neuroendocrine tumor. No significant hepatic or renal dysfunction was present in any patient. Table 1 provides a breakdown of the final diagnosis in each patient. All patients gave informed consent. The study was approved by the institutional review board and the radioactive drug research committee of Mayo Foundation.

Preparation of \(^{123}\)I-Octreotide

Tyr-octreotide was obtained from Sandoz Research Institute (Berne, Switzerland) and its purity confirmed by amino acid sequence and high-pressure liquid chromatography (HPLC). In the first 15 studies, the octreotide was labeled with \(^{123}\)I by the chloramine-T reaction (17) using the method of Bakker et al. (9). However, this led to large variations in labeling efficiency and modifications were made to previously published methods (9,18).

The principal modification was the use of \(^{123}\)I (Nordion Inter., Ontario, Canada) in dry form to increase its specific activity over that available in liquid form. The dry form of \(^{123}\)I had a specific activity of 500 Ci/mg and a radiochemical purity of > 99.8% at 24 hr post-processing. The dry \(^{123}\)I was dissolved in 50 \(\mu\)l 0.5 \(M\) phosphate-buffer solution and buffered to pH 7 using 1–2 N HCL. The Tyr-octreotide (42 \(\mu\)g in 60 \(\mu\)l of 0.05 \(M\) acetic acid) was added to the \(^{123}\)I solution and agitated for 30 sec. Radioio-
dination was initiated by the addition of chloramine-T solution (50 mg in 2 ml of 0.05 M phosphate buffer, pH 7.5–7.8) and the solution was vortexed for 1 min. To avoid nonspecific damage to the peptide, the optimum ratio of chloramine-T solution-to-\(^{123}\text{I}\) solution was found to be 1:235. Iodination was terminated by the addition of 1 ml human serum albumin (10%). After vortexing for 30 sec, 10 ml of 0.05 mM ammonium acetate was added.

### Purification and Quality Control of \(^{123}\text{I}\)-Octreotide

The \(^{123}\text{I}\)-octreotide iodination solution was purified using a Sep-Pak C18 cartridge (Waters Assoc, Milford, MA). The cartridge was prewet with 5 ml 70% ethanol and activated with 5 ml 2-propanol. After application of the solution, the cartridge was successively washed with 5 ml fractions of distilled H\(_2\)O, 0.5 M acetic acid and 96% ethanol. The ethanol fraction was evaporated at 40–50 °C under nitrogen flow and redissolved in 2–5 ml of 0.05 M acetic acid in 0.9% NaCl. The \(^{123}\text{I}\)-octreotide solution was then passed through a 0.2 mm filter (Acrodisc 13, Gelman Sciences, Ann Arbor, MI) prior to quality control and injection.

The \(^{123}\text{I}\)-octreotide preparation was analyzed using a reversed-phase column HPLC system as described previously (9). Eluant radioactivity was measured with a NaI probe connected to an analyzer (Model 427, Beckman Instruments, San Ramon, CA).

### Patient Preparation and Injection

All patients who were taking octreotide therapeutically were requested to discontinue treatment for a period of 3 wk prior to the start of the study. Five drops per day of Lugol's solution was administered 1 day prior to and for 3 days following the injection of \(^{123}\text{I}\)-octreotide. The injected activities were 13.1 ± 5.8 mCi (mean ± s.d.), with a range of 2.1 to 22.2 mCi, in the first 15 patients, and 18.5 ± 2.7 (mean ± s.d.) with a range of 14.7 to 24.0 mCi in the remaining 15 patients. Poor labeling efficiency and low injected activities lead to suboptimal image quality in two of the first 15 cases and analysis of these data has been excluded from the results. Depending upon the labeling efficiency, patients received less than 35 µg of radiolabeled octreotide. The radiopharmaceutical was injected via a peripheral arm vein over a 5-min period. Starting 4–6 hr after injection of the \(^{123}\text{I}\)-octreotide, four liters of Golytely were administered orally over a 2-4-hr period to aid in the clearance of radioactivity excreted into the bowel via the hepatobiliary system.

### Patient Imaging

Planar images were acquired using a dual-headed gamma camera system (Bodyscan, Siemens Gammasonics, Des Plaines, IL). The gamma camera heads were equipped with low-energy, high-resolution collimators and images were acquired using a 20% window centered on the 159 keV emission from \(^{123}\text{I}\). Following injection, images of the abdomen were acquired at 1 min/
where $S$ is the target organ dose-rate per unit of activity in each organ. The effective dose equivalent was calculated by the method of ICRP 26 (22).

In MIRDose, the dynamic bladder model was utilized with a voiding interval of 4.8 hr and the results compared to those obtained with the ROI data. MIRDose also allows the selection of a gastrointestinal (GI) kinetics model described in ICRP 30 (23). Normal GI kinetics were assumed and the ICRP kinetics model was utilized and compared to dose estimates computed from ROI data.

For all tumors, the height and width of the lesions were measured from the appropriate anterior or posterior image and tumor volume calculated by assuming a spherical, ellipsoidal or cylindrical shape for the lesion. It is recognized that this method is not ideal and provides, at best, a crude estimate of tumor volume.

With the assumption that the biological behavior of radioiodinated tyr-octreotide is independent of the isotope used, organ and tumor doses for $^{131}$I-octreotide were calculated from the biological data obtained from $^{123}$I-octreotide. For $^{131}$I, it was assumed that all beta energy (mean = 0.19 MeV) would be absorbed in the tumor. The beta dose, $R_b$, was calculated from the following equation:

$$R_b = 73.8 \times (0.19 \text{ MeV}) \times T_b,$$

where $T_b$ is the effective half-time, in days, of $^{131}$I in the tumors. For gamma rays, absorbed fractions were estimated from Table 8, MIRD Pamphlet 2 (24), for tumor sizes that approximate those in study patients and used to compute the gamma ray dose $R_g$ to the tumor. This dose was added to the beta absorbed dose for each tumor to give total tumor dose in g-rads/$\mu$Ci.

### RESULTS

#### Labeling Efficiency

In the first 15 patients, $33.7\% \pm 12.4\%$ was recovered as $^{123}$I-octreotide in the 96% ethanol solution. Hence, initial activities of 60 mCi $^{123}$I were required per study. With the modifications to the labeling procedure described above, the recovered activity increased to $65.6\% \pm 5.4\%$ in the remaining 15 patients, requiring an initial activity of only 30 mCi per study. HPLC analysis showed $99.2\% \pm 0.8\%$ of the injected activity to be $^{123}$I-octreotide.

#### Pharmacokinetics

Results from the 10 patients in whom complete blood and urine samples were obtained are presented in Figures 1–2. Figure 1 shows the percent injected $^{123}$I in whole blood and the initial hepatic uptake of $^{123}$I over the first 60 min postinjection. Activity left the vascular compartment with a calculated $T_h$ of 10 min with only 10% remaining after 1 hr. Thereafter blood activity decreased more slowly with approximately 4% present at 24 hours postinjection. Peak hepatic uptake occurred approximately 20 min postinjection and thereafter washed out with a $T_h$ of $105 \pm 35$ min (mean $\pm$ s.d.).

Figure 2 shows the whole body distribution of $^{123}$I-octreotide over a 40-hr period. The combined whole body and urine activity at 1 hr postinjection was considered to

![FIGURE 1. (A) Percent of the injected activity of $^{123}$I-octreotide in whole blood over the first hour postinjection. (B) Relative uptake of $^{123}$I-octreotide in the liver following injection (normalized to maximum hepatic activity for each subject).](image1)

![FIGURE 2. Distribution of $^{123}$I-octreotide in the whole body, urine and feces over the first 40 hr postinjection.](image2)
FIGURE 3. Anterior and posterior whole-body images taken at (A) 2 hr and (B) 40 hr postinjection illustrate the biodistribution of $^{123}$I-octreotide.

FIGURE 4. Mean values in 28 patients of the percent of the injected activity of $^{123}$I-octreotide in (A) the liver and gastrointestinal system and (B) the lungs, thyroid and genitourinary system over the first 40 hr postinjection.

FIGURE 5. (A) Anterior and posterior whole-body images at 4 hr postinjection. Uptake is seen in the mediastinum, the left supraclavicular region and the proximal right femur. (B) Bone scan demonstrates a focal area of increased uptake in the proximal right femur corresponding to the metastatic lesion seen on the $^{123}$I-octreotide scan.

onstrating the changing whole-body distribution of $^{123}$I-octreotide over time. On the 2-hr images (Fig. 3A), there was intense gallbladder activity along with activity in the liver, bladder, kidneys and lungs. There was no significant activity in the bone marrow or any other soft-tissue region. The 40-hr images (Fig. 3B) show activity primarily located in the large bowel, with activity still present in the liver and kidneys. Activity can also be seen in the thyroid. Thyroid uptake was seen on several patients despite adequate blockage with Lugol's solution. This may be due to the presence of somatostatin receptors in the thyroid gland.

The biodistribution of $^{123}$I-octreotide in the 28 patient studies is shown in Figure 4. Approximately 20%–30% appears in the liver and gastrointestinal system (Fig. 4A), with less than 4% in the kidney and bladder. Lung uptake was noted in the early (1–4 hr) images (Fig. 3), however the values of 3%–4% presented in Figure 4B may be an overestimation since no attenuation correction was applied to the data.

Figure 5A shows the $^{123}$I-octreotide images taken 4 hr postinjection in a patient who developed omental metastases 2 yr after resection of a small bowel carcinoma. The patient developed progressive carcinoid syndrome with extensive hepatic metastases seen on CT scan, which were also seen on SPECT somatostatin images (not shown). These lesions are just discernable as areas of irregular activity in Figure 5A. Uptake was also seen in the mediastinum, left supraclavicular region and right femur. A subsequent bone scan (Fig. 5B) confirmed the lesion in the right femur to be an osseous metastasis.

In the 28 patients, 22 had positive scans with uptake in hepatic tumors (17 patients) and nonhepatic tumors (10 patients). Three patients showed photon-deficient uptake in known tumor regions and three patients had negative scans. Estimated tumor volumes were $14.6 \pm 18.2$ g (range 0–59 g) for nonhepatic lesions and $385 \pm 433$ g (range 9–1130 g) for hepatic lesions. For analysis of washout of activity from tumors, the percent uptake of $^{123}$I-octreotide in 25 nonhepatic lesions and 6 hepatic lesions was measured over the 40-hr scanning period. Figure 6 indicates that washout of activity from tumors was similar for both liver and skeletal tumors.
hepatic and nonhepatic lesions, with a biological half-time of approximately 15 hr for hepatic tumors and 22 hr for nonhepatic tumors. However, tumor uptake per gram of tissue was greater (by a factor of approximately 6–7) in nonhepatic lesions as compared to hepatic lesions.

**Dosimetry**

Table 2 presents the absorbed dose estimates in various organs and the effective dose for 131I-octreotide. The highest dose is to the gallbladder wall with an absorbed dose of approximately 0.5 rad/mCi. Results obtained using the MIRDOSOSE bladder model gave a dose of 0.066 rad/mCi to the bladder wall. This value compares well with the value of 0.068 rad/mCi obtained from the ROI data. The ICRP model of GI kinetics gave dose estimates to the upper and lower large intestine, which were approximately an order of magnitude larger than those computed from the ROI data (Table 2). The mean effective dose for the 28 studies was in the range 0.07–0.22 rem/mCi, which compares favorably with other radiopharmaceuticals.

Tumor dose (data not shown) varied with tumor location (hepatic versus nonhepatic) and was reduced by a factor of 3 in large hepatic lesions (>150 ml) relative to nonhepatic lesions. The tumor doses ranged between 0.1–0.6 rad/mCi, which are not significantly larger than the dose to the gallbladder.

Table 3 presents the dose estimates to the body from 131I-octreotide, calculated using the biological data from 131I-octreotide. From the ROI data, the highest dose is to the gallbladder wall, which receives a dose of 2.2 rad/mCi. Under conditions where normal GI kinetics are applicable, the highest dose is to the lower large intestine, which receives a dose of 16.4 rad/mCi.

Table 4 shows the calculated absorbed dose to tumors for 131I-octreotide, expressed as g-rads per µCi of activity in the tumor. Using average tumor volumes of 20 g and 350 g, and uptakes of 5.5% and 0.8% per 100 g tumor

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**TABLE 2**

<table>
<thead>
<tr>
<th>Target organ</th>
<th>ROI rad/mCi</th>
<th>GI/DBM rad/mCi</th>
</tr>
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<tbody>
<tr>
<td>Gallbladder wall</td>
<td>0.48</td>
<td>0.53</td>
</tr>
<tr>
<td>Liver</td>
<td>0.10</td>
<td>0.11</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.11</td>
<td>0.32</td>
</tr>
<tr>
<td>Upper large intestine</td>
<td>0.10</td>
<td>0.77</td>
</tr>
<tr>
<td>Lower large intestine</td>
<td>0.08</td>
<td>0.86</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Urinary bladder wall</td>
<td>0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Breast</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.06</td>
<td>0.19</td>
</tr>
<tr>
<td>Testes</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.06</td>
<td>0.07</td>
</tr>
</tbody>
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**TABLE 3**

<table>
<thead>
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<th>Target organ</th>
<th>ROI</th>
<th>GI/DBM</th>
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</thead>
<tbody>
<tr>
<td>Gallbladder wall</td>
<td>2.17</td>
<td>2.37</td>
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<tr>
<td>Liver</td>
<td>0.33</td>
<td>0.39</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.44</td>
<td>1.67</td>
</tr>
<tr>
<td>Upper large intestine</td>
<td>0.32</td>
<td>6.40</td>
</tr>
<tr>
<td>Lower large intestine</td>
<td>0.32</td>
<td>16.40</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.49</td>
<td>0.58</td>
</tr>
<tr>
<td>Urinary bladder wall</td>
<td>0.46</td>
<td>0.69</td>
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<tr>
<td>Thyroid</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.22</td>
<td>0.22</td>
</tr>
<tr>
<td>Breast</td>
<td>0.09</td>
<td>0.09</td>
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<tr>
<td>Ovaries</td>
<td>0.15</td>
<td>0.83</td>
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<td>Testes</td>
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<td>0.16</td>
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<tr>
<td>Red marrow</td>
<td>0.25</td>
<td>0.13</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.17</td>
<td>0.11</td>
</tr>
</tbody>
</table>

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**TABLE 4**

<table>
<thead>
<tr>
<th>Tumor size (g)</th>
<th>Hepatic tumors</th>
<th>Nonhepatic tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R₀</td>
<td>R₁/₂</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>8.8</td>
</tr>
<tr>
<td>20</td>
<td>0.9</td>
<td>9.5</td>
</tr>
<tr>
<td>50</td>
<td>1.1</td>
<td>9.7</td>
</tr>
<tr>
<td>150</td>
<td>1.5</td>
<td>10.1</td>
</tr>
<tr>
<td>350</td>
<td>2.1</td>
<td>10.7</td>
</tr>
<tr>
<td>700</td>
<td>2.6</td>
<td>11.2</td>
</tr>
<tr>
<td>1100</td>
<td>3.0</td>
<td>11.6</td>
</tr>
</tbody>
</table>

Largest nonhepatic tumor was 59 g.
tissue for nonhepatic and hepatic tumors respectively, the average tumor doses were calculated to be 5 rad/mCi and 0.9 rad/mCi for nonhepatic and hepatic lesions, respectively. These tumor doses are of the same order of magnitude as doses to target organs.

**DISCUSSION**

A review of our labeling procedure indicated that the radiiodination of tyr-octreotide was best performed in a small volume (30–200 μl) to permit efficient radiiodination of minute amounts of protein/peptide. Bakker et al. (9) observed some instances of low labeling yields (<5%) with 123I-octreotide which they attributed to other iodine impurities and the low specific activity of 123I (<100 Ci/mg). We experienced similar problems, which were resolved by the use of very high specific activity 123I. The high peptide-to-iodine ratio (4200:1) not only favors a higher radiiodination, but also avoids the formation of di-iodinated tyr-octreotide (9). Furthermore, the concentration and duration of exposure of the tyr-octreotide to chloramine-T was kept to a minimum to avoid nonspecific damage to the protein/peptide.

The HPLC analysis indicated that the radiiodinated peptide separated by SEP-PAK C18 cartridge contained very high purity 123I-octreotide. This suggests that SEP-PAK C18 chromatography can be utilized for the purification and quality control of 123I-octreotide without the additional need of using a HPLC system.

While the initial in vivo behavior of 123I-octreotide as shown in Figure 1 is similar to that reported by Bakker et al. (12), we found significant differences in the pathway by which the radiolabeled somatostatin was eliminated from the body. The study of Bakker et al. (12) found a high urinary excretion (approximately 45% in the first 30 hr) with little or no fecal excretion of the 123I-octreotide in patients with normal gastrointestinal function (i.e., no previous intestinal operations). They concluded that the radiolabeled octreotide was hydrolyzed in the intestines and the degradation products reabsorbed. In contrast, our results indicated that fecal excretion accounted for 55% of the administered dose over the first 40 hr, with only 15%–20% accounted for by urinary excretion (Fig. 4). Activity in the large bowel was commonly observed in the 16- and 40-hr images (Fig. 3), and could sometimes be seen in the 4-hr images (Fig. 6). The main reason for these discrepancies may be due to the use in this study of a cathartic (Golytely) that induced water diarrhea and would have shortened the residence time of radioactivity in the small and large bowel. This shortened residence time would also have reduced the degree to which the 123I-octreotide could be hydrolyzed and reabsorbed in the intestines.

The use of simultaneous anterior and posterior whole-body imaging permitted a more accurate estimate of the biodistribution of 123I-octreotide than previously reported (12). While most activity was localized in the GI system, uptake was also seen in the genitourinary system and in the lungs (Fig. 3). At present, we do not have a satisfactory explanation for this pulmonary uptake. Dose estimates to various organs in the body, based on ROI data, indicate that the highest dose is to the gallbladder wall which receives a dose of 480 mrad/mCi (Table 2). This is in good agreement with the value of 440 mrad/mCi obtained by Bakker et al. (12). The GI kinetic model from ICRP 30 indicates that the highest dose should be to the upper and lower large intestine, which would receive approximately 800 mrad/mCi (Table 2). This more conservative dose estimate assumes that normal gastrointestinal kinetics are applicable. However, due to the administration of a cathartic, our results would indicate that gastrointestinal transit is more rapid than normal and consequently the ICRP 30 kinetic model is not applicable in this study. Hence, the use of a cathartic has two primary benefits in 123I-octreotide scintigraphy: reduced background activity in the abdominal region and a major reduction in the radiation dose to the small and large intestines.

The uptake and washout of 123I-octreotide in tumors was very similar to that seen in the liver and gastrointestinal tract, with the maximum uptake occurring between 1–4 hr postinjection. We found a significant difference in the absolute uptake of 123I-octreotide by hepatic and nonhepatic tumors (Fig. 6). This may be due to differences in tumor cell density in hepatic versus nonhepatic lesions. The results presented in Tables 3 and 4 indicate that the average tumor dose with 131I-octreotide is of the same order of magnitude as doses to the gallbladder, kidneys and thyroid, due to the similarity in kinetics of 123I-octreotide in normal body organs and in tumors. Hence, the therapeutic application of tyr-octreotide labeled with 131I or 123I does not appear feasible. It is possible that other formulations of radiolabeled somatostatin, with longer tumor retention times, may have potential therapeutic applications.

The feasibility of labeling somatostatin or an analog of somatostatin with other radioisotopes has been investigated by several groups, and initial studies with both 111In (25,26) and 99mTc-labeled analog of somatostatin (27) have shown promising results. In particular, results with 111In-DTPA-octreotide have indicated that this agent may be superior to 123I-octreotide, due to reduced background activity in the abdomen and consequential improvement in the visualization of abdominal lesions (26).

In conclusion, we have found that 123I-octreotide is a useful agent for the visualization of neuroendocrine tumors. It demonstrates a favorable dosimetry, comparable to many existing diagnostic radiopharmaceuticals. Its rapid uptake permits imaging within 1–4 hr postinjection. However, the rapid washout of this agent from the tumor site precludes the possible therapeutic applications of tyr-octreotide radiolabeled with isotopes such as 131I or 123I.

**REFERENCES**


**CORRECTION**

In the July issue of the Journal, the title of the article by Mehta et al. (pages 1373–1377) was printed incorrectly. The corrected title is: In-Vivo Identification of Tumor Multidrug Resistance with $^3$H-Colchicine.

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