Imaging the Adrenal Glands with Radiolabeled Inhibitors of Enzymes: Concise Communication


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Although radioiodinated cholesterol furnished the first noninvasive imaging of the adrenal glands, it would be desirable to decrease the time for imaging and decrease the radiation dose. The relative tissue distributions of two radiolabeled enzyme inhibitors [3H] metyrapol and I-125-SKF-12185 were studied in dogs and man. Their percentage uptakes and target-to-nontarget ratios were similar. The adrenals of three dogs were imaged sharply at 2 hr after injection with 4–6 mCi of I-131-SKF-12185, confirmed by subsequent imaging with 1 mCi of I-131-6-beta-19-nor cholesterol at 5 days after injection. The use of 1 mCi of I-123-SKF will permit imaging of the adrenals in 1–2 hr and will decrease the radiation dose in the human to 0.76 rads to the adrenal, 0.18 rads to the ovaries and 1.7 rads to the liver.


METHODS

Although radioiodinated cholesterol (1–4) have furnished the first noninvasive imaging of the adrenal glands, it would be desirable to decrease the time required and the radiation dose delivered by this procedure. We have reported the first syntheses (5) and tissue distribution studies of H-3- and I-125-labeled reversible enzyme inhibitors in rats and dogs (6). We now report the tissue distribution of [3H] metyrapol and I-125-SKF-12185 in humans, and clear imaging of the dog adrenals with I-131-SKF-12185.

Radiolabeled compounds. The chemical structures of [3H] metyrapol and I-125-SKF-12185 are presented in Fig. 1. The [3H] metyrapol was obtained by sodium borohydride reduction of [3H] metyrapone, and was purified in our laboratory by column chromatography on silica gel-G. The specific activity was approximately 200 mCi/mM. The radiochemical purity was greater than 98% as determined by thin-layer chromatography on silica gel-G.

The [131I] iodo-SKF-12185 was obtained by radioiodination of SKF-12185 using Chloramine T. The specific activity of the product ranged from 40 to 100 mCi/mM. The final reaction mixture was passed through an anion-exchange column to remove free iodide, evaporated to dryness, then reconstituted as the dihydrochloride salt in a solution of 1.6% Tween 80, 6.6% absolute ethanol, and q.s. normal saline. This final formulation was then passed through a sterile, pyrogenic 0.22 micron filter. The radiochemical purity was greater than 96% as determined by thin-layer chromatography.

The corresponding stable-iodine compound was characterized by infrared and nuclear magnetic resonance spectroscopy and the expected carbon, hydrogen, and nitrogen analyses.

Injected volumes varied over 1–2 ml. Sterility was checked by means of radiometric bacterial test and freedom from pyrogens by the Limulus lysate test.

Patients. Eight patients scheduled for adrenalec-
tomy (for primary aldosteronism, pheochromocytoma, or breast carcinoma) received 100 μCi each of [3H] metyrapol or I-125-SKF-12185 (I-125-SKF) intravenously 1–2 hr before excision of the adrenals. The aldosterone patients had each been given 50 mg of cortisol acetate i.m. 1 hr before surgery. The patients with pheochromocytomas had an additional 50 mg 8 hr preoperatively. The breast carcinoma patients were given 50 mg 8 hr before and 100 mg 1 hr before surgery. We have preliminary data that cortisol acetate given before the tracer dose of radio-labeled enzyme inhibitor depresses the adrenal uptake of the inhibitor. Samples of adjacent tissues and blood were taken for comparison. Representative tissue samples, weighing 30–50 mg were placed in counting vials containing 0.3 ml of 10% NaOH, left to digest overnight, and dissolved by warming to 70°C. After cooling, the samples were neutralized with 2 drops of glacial acetic acid, decolorized with 3–6 drops of 30% hydrogen peroxide and vortexed. Ten milliliters of liquid-scintillation fluid and 2.5 ml of distilled water were added to each vial, which was again vortexed. After cold and dark adaptation, the samples were counted for 10 min in a liquid-scintillation system. Quench corrections were made using the channels-ratio counting technique. Tissue concentrations were expressed as percent kilogram dose per gram (% kg dose/g), calculated as follows (7):

\[
\frac{\muCi \text{ tissue} \times \text{kg body wt} \times 100}{\muCi \text{ administered dose}}
\]

**Dogs.** Three mongrel dogs weighing 15–20 kg were each given a dose of 4–6 mCi (1 mCi/kg) of I-131-SKF intravenously. This activity was used to simulate the photon flux expected at an Anger camera crystal with 2 mCi of I-123-SKF. Posterior images were obtained continuously from 10 min to 3 hr using a gamma camera with a high energy collimator, interfaced to a mini-computer. The dogs were in the prone position, under i.v. sodium pentobarbital anesthesia.

One week later the same dogs were injected with 1 mCi of 6-beta-iodomethyl-19-norcholesterol (NP-59) intravenously and the adrenals were imaged at 5 days after this tracer dose for comparison with the I-131-SKF imaging of the adrenals in the same dog.

**RESULTS**

**Humans.** Table 1 shows the tissue distribution of [3H] metyrapol in five patients (% kg dose/g). A mean adrenal uptake of [3H] metyrapol of 5.9% (four patients) occurred in 1 hr. Blood, muscle, and fat were 1.0% or less. At 2 hr, adrenal was 3.3%

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**TABLE 1. TISSUE DISTRIBUTION OF [3H] METYRAPOL IN HUMANS (% KG-DOSE/G)*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary aldosterone</th>
<th>Phaeochromocytoma</th>
<th>Breast carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Time Interval (hr)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adrenal</td>
<td>8.88</td>
<td>4.72</td>
<td>4.14</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>4.36</td>
<td>3.26</td>
<td>7.54</td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>3.33</td>
<td>0.82</td>
<td>5.40</td>
</tr>
<tr>
<td>Tumor</td>
<td>8.05</td>
<td>0.38</td>
<td>0.04</td>
</tr>
<tr>
<td>Adipose</td>
<td>0.27</td>
<td>0.06</td>
<td>0.15</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.57</td>
<td>0.38</td>
<td>0.21</td>
</tr>
<tr>
<td>Blood</td>
<td>0.65</td>
<td>0.15</td>
<td>1.54</td>
</tr>
<tr>
<td>Liver</td>
<td>0.65</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

* Dose: 100 μCi i.v.
TABLE 2. TISSUE DISTRIBUTION STUDY OF I-125-SKF-12185 IN HUMANS (% KG-DOSE/G)^*  

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aldo/2o</td>
<td>adrenal</td>
</tr>
<tr>
<td>Patient No. 1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Time interval (hr)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tumor</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Whole adrenal</td>
<td>0.99</td>
<td>—</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>0.81</td>
<td>0.67</td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>2.92</td>
<td>1.15</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>Blood</td>
<td>—</td>
<td>0.04</td>
</tr>
<tr>
<td>Bone</td>
<td>—</td>
<td>0.08</td>
</tr>
</tbody>
</table>

^* Dose: 100 µCi i.v.

The dose of 4–6 mCi of I-131-SKF was used to simulate photon flux at the crystal expected with 2 mCi of I-123-SKF. The calculated radiation doses 2 mCi of I-123-SKF, in humans are adrenals 0.76, ovaries 0.18, and liver 0.68, all in rads. The dosimetry calculations are based on the tissue distribution of I-125-SKF in dogs as performed in our laboratory. Cumulated activity was determined for each source organ based on biologic turnover. Any uptake component of the distribution was ignored since the time for uptake was very short compared with excretion times. It is assumed that I-123-SKF behaves in vivo exactly like I-125-SKF and that tissue distribution in humans will be similar to that of the dog. It is also assumed that the activity is uniformly distributed in the source organs. The I-123 currently utilized in the synthesis of this agent has a radionuclidic purity of greater than 99.6% at the time of manufacturer's calibration. The dosimetry estimates presented are based on pure I-123 and do not consider the presence of the less than 0.4% I-125 impurity at the time of calibration.

The two limitations to more routine use of [I] iodocholesterols are: the period of days required to complete adrenal imaging, and the larger than desirable radiation dose delivered to the adrenals and gonads.

The peak radiotracer uptake at 2 hr from these labeled enzyme inhibitors, and the <1 hr synthesis time makes possible the use of I-123-SKF more effectively with the Anger camera in a shorter period of time and with a lower radiation dose. When necessary for higher-resolution collimation, a large dose with greater photon flux would aid the imaging of smaller adrenal tumors.

ACKNOWLEDGMENTS

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REFERENCES


THE SOCIETY OF NUCLEAR MEDICINE
25th ANNUAL MEETING
June 27–30, 1978
Anaheim Convention Center
Anaheim, California

SECOND CALL FOR ABSTRACTS FOR SCIENTIFIC PROGRAM

The Scientific Program Committee solicits the submission of abstracts from members and nonmembers of the Society of Nuclear Medicine for the 25th Annual Meeting of the Society of Nuclear Medicine. Original contributions in four specified categories (Clinical Science, Basic Science, In Vitro and Correlative Techniques, Clinical Practice) on a variety of topics related to nuclear medicine will be considered, including:

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Computed Tomography
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Dosimetry/ Radiobiology
Endocrine/ Metabolism
Gastroenterology
Hematology

Instrumentation
In Vitro Studies/ Radioassays
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Oncology
Pediatrics
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Radiotherapeutics
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Ultrasound

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