INVESTIGATIVE NUCLEAR MEDICINE

Myocardial Imaging in Man with I-123 Meta-Iodobenzylguanidine

Robert C. Kline, Dennis P. Swanson, Donald M. Wieland, James H. Thrall, Milton D. Gross, Bertram Pitt, and William H. Beierwaltes

University of Michigan Medical Center, Ann Arbor, Michigan

Meta-[123I]iodobenzylguanidine (m-[123I]IBG), a guanethidine analog, was used to image the myocardium in five normal male volunteers. Each subject received 2.0 mCi m-[123I]IBG intravenously. Four were given a bolus injection. Multiple myocardial scintigrams were obtained over a 2-hr period. Myocardial uptake was calculated by dividing the decay-corrected global myocardial count rate (after interpolated background correction) by the peak count rate during the first passage of the m-[123I]IBG bolus through the heart. The left ventricle could be visualized within 1–2 min of m-[123I]IBG injection. Mean myocardial uptake was 0.63% (range 0.45–0.78 %) of injected dose at 5 min, and 0.76% (range 0.49–0.93 %) at 2 hr (n = 4). m-[123I]IBG may provide quantitative information on myocardial catecholamine content.


Tracer studies in animals with norepinephrine labeled with H-3 or C-14 have shown its rapid localization in the heart (1,2). Since myocardial norepinephrine concentration is altered in a variety of pathologic conditions (3), myocardial imaging with norepinephrine or a norepinephrine analog could prove to be of considerable diagnostic utility. Carbon-11 norepinephrine has been used to image the canine myocardium (4), but the use of such an agent is limited by the need for both a cyclotron and a positron camera on site. An agent that is more readily available and is compatible with conventional single-photon cameras would be of greater practical use.

Meta-[123I]iodobenzylguanidine (m-[123I]IBG), an analog of the adrenergic-neuron-blocking agent guanethidine (Fig. 1), has recently been used to image the heart in the dog and the rhesus monkey (5). The mechanism of uptake has not been fully elucidated, but initial studies suggest that m-[123I]IBG may be stored in adrenergic neurons by the same mechanism as that for norepinephrine (5). We report our initial use of this agent in five normal human volunteers.

METHODS

Iodine-123 produced by the 127I (p,5n) 123Xe → 123I reaction was obtained commercially. Meta-[123I]iodobenzylguanidine (m-[123I]IBG) was prepared by a method similar to that reported for meta-[125I]iodobenzylguanidine (6). The final product was formulated in bacteriostatic 0.9% saline, buffered to pH 6.0 with...
sodium acetate. Radionuclidic purity, determined using a low-energy, lithium-drifted germanium gamma detector, was always greater than 99% at calibration. Free iodide content was always less than 2%, as assessed by radioactive thin layer chromatography (silica gel G with ethyl acetate:ethanol, 1:1). Specific activity averaged 5.0 mCi/mg at a calibration time immediately after synthesis. Tests for pyrogens and bacterial contamination were uniformly negative.

Informed consent was obtained from five male volunteers, ages 23–31 yr. All were normal by history, physical examination, electrocardiogram, and laboratory screening panel. To block thyroidal uptake of free I-123, all were given Lugol's solution U.S.P., three drops twice daily, for 1 day before and 2 days after imaging. Vital signs and electrocardiograms were monitored before, during, and after injection of the tracer. Electrocardiograms and laboratory screening panels were repeated 24 hr after m-\([^{123}\text{I}]\)IBG injection.

Each subject was given 2.0 mCi m-\([^{123}\text{I}]\)IBG by antecubital vein. Four were given the dose as a bolus. All data were recorded onto a dedicated nuclear medicine minicomputer for display, video formatting, and quantitative analysis. Cardiac imaging was performed in a 40° left anterior oblique projection, using a standard-field gamma camera equipped with a low-energy, high-sensitivity collimator. A 25% window was used, centered at 159 keV. A 60-sec dynamic acquisition at one frame/sec was begun simultaneously with the m-\([^{123}\text{I}]\)IBG injection. Five-minute images were acquired sequentially for 60 min, and again at 90 and 120 min. Additional 50,000-count images were obtained on a wide-field gamma camera with pinhole collimation.

From the initial 60-sec flow study, time-activity curves were generated from the entire detector field of view except the outer three pixels (to avoid edge packing). The curves were inspected in conjunction with the images to determine the count rate during the frame with maximum activity in the heart. This count rate was taken to represent 100% of the injected dose.

Background correction of static images was obtained using the interpolation technique described by Goris (7) and modified by Watson and Beller (8). Myocardial percent uptake was calculated by dividing the decay-corrected net myocardial count rate following background correction by the count rate during the first passage of the m-\([^{123}\text{I}]\)IBG bolus. Since the technique is not applicable with a poor bolus, the images and curves were inspected to ensure adequacy of the bolus as it reached the heart. Each of the four subjects studied in this fashion received a compact bolus. Heart-to-lung and heart-to-liver ratios were calculated from normalized regions of interest selected by light pen from the unprocessed images.

To determine the elimination kinetics of m-\([^{123}\text{I}]\)IBG, blood, urine, and feces were collected at preselected intervals and analyzed for radioactivity. Radiation dosimetry estimates (Table 1), initially calculated from animal distribution studies using m-IBG tagged with I-125 and I-131 (9), were modified for the heart and whole body according to human uptake and clearance data.

**RESULTS**

The left-ventricular myocardium could be visualized

<table>
<thead>
<tr>
<th>TABLE 1. ESTIMATED RADIATION DOSIMETRY*† FOR META-[(^{123}\text{I})]IODOBENZYLGUANIDINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Adrenal medulla</td>
</tr>
<tr>
<td>Ovary (testes)</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Spleen</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Heart</td>
</tr>
<tr>
<td>Whole body</td>
</tr>
</tbody>
</table>

* Based on dog distribution studies.
† Assume pure I-123.

To unblock thyroid. Radiation dose to thyroid resulting from I-123 as iodide, liberated in vivo, will be further reduced by administration of Lugol's iodine.

**FIG. 2.** m-\([^{123}\text{I}]\)IBG images of myocardium in five normal volunteers, acquired over 15 min in the 40° LAO projection. (A) unprocessed digital images. (B) images after interpolated background subtraction.
within 1-2 min of $m^{-[123I]}$IBG injection. Uptake in the upper septum and base appeared less than in other wall segments, and apical thinning was prominent in two subjects. Otherwise the images (Fig. 2) were qualitatively similar to those produced by perfusion agents. Mean myocardial uptake was 0.63% (range 0.45-0.78%) of injected dose at 5 min, increasing to 0.76% (range 0.49-0.93%) at 2 hr (n = 4, Fig. 3). Mean heart-to-lung ratio was 1.17 at 5 min, increasing to 1.44 at 2 hr (Fig. 4A), and the corresponding heart-to-liver ratios were 0.78 and 0.60 (Fig. 4B). Images obtained with a pinhole collimator at 135 min showed significantly improved target-to-background (Fig. 5).

No significant side effects from $m^{-[123I]}$IBG administration were encountered. One subject noted a transient (~5 sec) feeling of lightheadedness when the bolus was injected, and another reported a brief metallic taste. No changes in cardiac rhythm or vital signs were found in any subject. Repeat electrocardiogram and laboratory test panel at 24 hr remained normal in all subjects.

Blood clearance of $m^{-[123I]}$IBG was rapid (Fig. 6). Mean urinary excretion was 64% (range 53-70%) over the first 24 hr (Fig. 7). Twenty-four-hour fecal collections, obtained in two subjects, contained 0.06% and 1.68% of the injected dose. Estimated radiation dosimetry based upon the human distribution data for $m^{-[123I]}$IBG was 0.03 rad/mCi for the heart and 0.03 rad/mCi for the whole body.

**DISCUSSION**

This study demonstrates that $m^{-[123I]}$iodobenzylanilideguanidine ($m^{-[123I]}$IBG) can be used for myocardial imaging in man. The clinical role of this new radiotracer remains to be defined. Our goal is not to develop a replacement for the perfusion agent T1-201, but to explore the possibility that $m^{-[123I]}$IBG uptake can be used to reflect myocardial catecholamine content quantitatively. If so, the agent could prove useful in the evaluation of such conditions as congestive heart failure, ventricular hypertrophy, autonomic denervation, and hyperthyroidism, all of which have altered myocardial catecholamine stores (3). Before such applications can be attempted, the dependence of $m^{-[123I]}$IBG images on myocardial perfusion, nonspecific uptake, and specific norepinephrine-like uptake must be determined as functions of time.

Other investigators have reported upon the potential of radiolabeled beta-adrenergic-receptor binding agents for myocardial imaging (10). Application of these agents has been difficult because successful imaging requires
compounds with very high specific activity in order to avoid saturation of binding sites having high affinity but low capacity. In contrast, since the catecholamine storage vesicles have a very high capacity, a radiopharmaceutical with the same storage pattern as norepinephrine could be a successful imaging agent without satisfying such stringent requirements for high specific activity.

Accurate quantitation of myocardial uptake is critical to the ultimate clinical application of \( m\-[\text{\textsuperscript{123}}\text{I}]\text{IBG}\). Our method for calculating uptake assumes that (a) all the initially injected activity is within the region of interest selected over the chest for determination of the 100% injected dose value; (b) internal distribution is such that attenuation is similar for the bolus and the delayed images; (c) background can be subtracted with acceptable accuracy; and (d) camera deadtime is not a significant factor. As the procedure has been performed, a compact bolus satisfies conditions (a) and (b). The interpolated background subtraction technique is felt to be the best method currently available for meeting condition (c). Finally, the 2-mCi bolus results in negligible deadtime with the modern gamma camera, satisfying condition (d).

In summary, \( m\-[\text{\textsuperscript{123}}\text{I}]\text{IBG}\) is a new agent for human myocardial imaging that may provide quantitative information on myocardial catecholamine content. With its 1-123 label, this radiopharmaceutical can be used without special equipment in a typical nuclear medicine laboratory.

**ACCEPTED REFERENCES**


---

**FOOTNOTE**

† Crocker Nuclear Laboratory, Davis, CA.

**ACKNOWLEDGMENTS**

This work was supported in part by NIH Grant No. 1-P01-NS-15655-01, DOE Grant No. EY-76-S-02-3031, NCI Grant No. CA-09015-05, and NIH Grant No. 1-R01-AM-21477-02.

The authors thank Thomas J. Mangner and Holly Anderson-Davis for synthesizing \( m\-[\text{\textsuperscript{123}}\text{I}]\text{IBG}\); Kathleen Worthington, and Laura Meyers for their technical assistance; Linder Markham for her help in preparing this manuscript; and John D. Jones and Dr. William Kerr for the use of their laboratories in the Phoenix Memorial Laboratory.

**REFERENCES**


---

**NUCLEAR MEDICINE HOTLINE**

A Hotline is available for technologists looking for positions and for employers seeking applicants in the greater New York area. The "Hotline" is:

(516) 679-9268

Physicians interested in employment, or those seeking employees, should contact Dr. Philip Bardfeld at: (516) 542-2674.

Physicists and radiochemists should contact Dr. Marilyn Noz at: (212) 679-3200, ext. 3638.