# Portrayal of Pheochromocytoma and Normal Human Adrenal Medulla by *m*-[$^{123}$I]Iodobenzylguanidine: Concise Communication

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**The radiopharmaceutical *m*-[$^{131}$I]iodobenzylguanidine (I-131 MIBG), which is readily taken up by adrenergic vesicles, produces scintigraphic images of pheochromocytomas in man but rarely visualizes normal adrenal glands. Iodine-123 has many potential advantages over I-131 as a radiolabel for MIBG, including shorter half-life, freedom from beta emissions, and increased gamma-camera efficiency. In this study, diagnostic doses of MIBG labeled with I-131 and I-123, with nearly equivalent radiation dosimetry, were compared as imaging agents in eight patients with known or suspected pheochromocytoma. Images of superior quality were obtained with I-123 MIBG, and lesions not visualized using I-131 MIBG were portrayed. In addition, the normal adrenal medullae were visualized on the I-123 MIBG scintigrams in six out of eight patients.**

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The adrenergic tumor-seeking radiopharmaceutical *m*-iodobenzylguanidine (MIBG) has been shown to image the normal canine and primate adrenal medulla when labeled with I-131 or I-123 (*1–4*). In man, pheochromocytomas have been portrayed using I-131 MIBG scintigraphy. Visualized lesions include benign adrenal (*5,6*), and extraadrenal primary (*5–8*) and malignant metastatic pheochromocytomas (*5,6,9*). In addition, increased adrenal I-131 MIBG uptake occurs with medullary hyperplasia of the multiple endocrine neoplasia syndrome Type 2 (MEN Type 2) (*10*). The technique, however, is not perfect and there is an approximately 10% false-negative rate (*6,11*). These studies, performed with 0.5 mCi I-131 MIBG (or 0.5 mCi I-131 MIBG per 1.73 m$^2$ of surface area for smaller patients), seldom (<20%) visualized the normal adrenal medullae, and then only faintly (*11*). The probable reason for this lack of adrenal visualization is the dose/kg body weight, which in man averaged 7 $\mu$Ci/kg compared with 60 $\mu$Ci/kg in dogs and 130 $\mu$Ci/kg in monkeys (*1,2,11*). The greater thickness of tissue overlying the adrenal glands in man may also contribute to their nonvisualization.

Iodine-123 has many potential advantages over I-131 as a radiolabel for MIBG, including better radiation dosimetry per $\mu$Ci administered (*12*) and a greater sensitivity of gamma cameras to I-123 emissions. These considerations led to a comparison of the results of I-131- and I-123-MIBG scintigraphy performed at dosage levels producing approximately equivalent tissue burdens in eight patients with known or suspected pheochromocytoma.

## METHODS

Of the eight patients, three had malignant metastatic pheochromocytoma, one a primary left-atrial pheochromocytoma, one a left pararenal tumor, two had no sign of recurrent disease after resection of a paraadrenal pheochromocytoma, and one had hypertension of nonpheochromocytoma origin. They were studied with both

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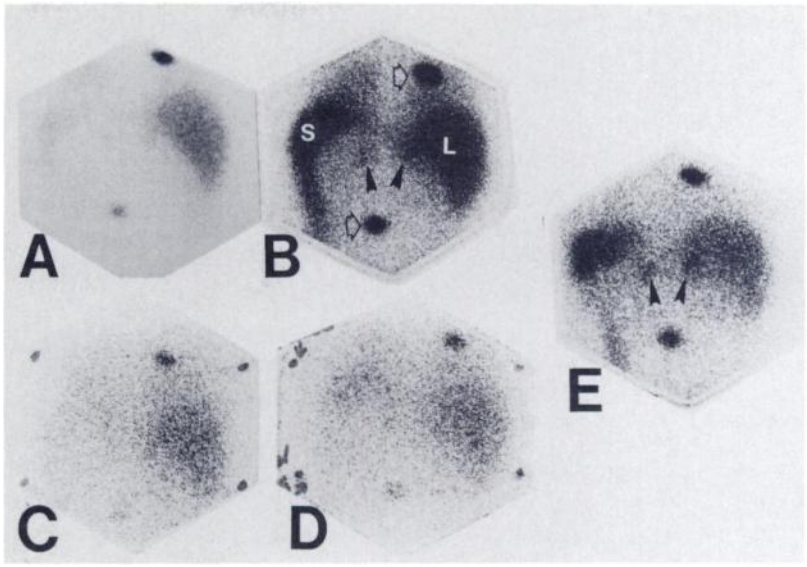


**FIG. 1.** Patient 1, posterior abdominal I-MIBG images: (A) 10 mCi I-123 MIBG imaged at 24 hr, 484 Kcounts, 3.5 min; (B) 10 mCi I-131 MIBG imaged at 48 hr, 404 K counts, 15 min; (C) 0.5 mCi I-131 MIBG imaged at 24 hr, 100 Kcounts, 12 min; (D) 0.5 mCi I-131 MIBG imaged at 48 hr, 100 Kcounts, 20 min; (E) 179 mCi I-131 MIBG imaged at 6 days, 200 Kcounts, 1.5 min. Arrowheads indicate adrenal glands, open arrows metastatic lesions. L = liver, S = spleen.

I-131 and I-123 MIBG. The I-131 studies were performed with 0.5 mCi I-131 MIBG, as previously described (*5,6*). The scintigrams were obtained at 24, 48, and 72 hr with a wide-field-of-view Anger camera, with a 30% window at 365 keV and a high-energy parallel collimator. In addition, scintigrams were obtained with a therapeutic dose of I-131 MIBG (173 mCi, 5.53 mg) in Patient 1 (*13,14*), beginning at 6 days, since the patient was isolated following the administration.

Iodine-123 MIBG scintigrams obtained with approximately 10 mCi I-123 MIBG (mean specific activity 8.7 mCi/mg, range 6.5–11.7) were performed as in the I-131 MIBG studies, using the same collimator but with a 20% window centered at 159 keV. Initial images were made as early as 2.5 hr. In some patients the I-131 and I-123 MIBG studies were performed simultaneously. Syntheses of I-131 MIBG and I-123 MIBG were reported previously (*1–4*). The I-123 for these syntheses was produced by the *p,5n* reaction, with specification of a maximum I-125 impurity of 1.4% at time of calibration.

In all instances, thyroid blockade of free radioiodine uptake was achieved by the administration of a saturated solution of potassium iodide, one drop t.i.d., begun 1 day before and through 7 days after tracer administration in the case of diagnostic doses, and for 30 days in the case of therapeutic doses (*15*).

**Subjects.** Patient 1 was a 33-yr-old male with pheochromocytoma metastatic to bone. I-131 MIBG scintigrams revealed metastatic lesions in the skull, lumbar spine, and a posterior rib. His primary tumor had been excised. Because of metastatic disease, he received therapeutic doses of 91.7 and 173 mCi I-131 MIBG. These therapeutic doses did not affect the lesions' ability to take up I-131 MIBG in subsequent 0.5 mCi diagnostic I-131 MIBG scintigrams or reduce tumor size on radiographs, but it did reduce plasma and urinary catecholamines to approximately 50% of pretherapy values. Figure 1 shows representative views of the posterior abdomen, comparing posttherapeutic scintigrams obtained with 0.5 mCi I-131 MIBG and 10 mCi I-123 MIBG, as well as the therapeutic dose of 173 mCi I-131 MIBG.

Patient 2 was a 37-yr-old female who presented with a large paraaortic pheochromocytoma, with destruction of the left acetabulum by a skeletal metastasis. The primary tumor was resected but a small amount of residual tumor was thought to have remained in the tumor bed. Figure 2 shows multiple foci of residual tumor, which are seen only in the I-123 MIBG study. A skeletal metastasis is demonstrated by both I-131 and I-123 MIBG.

Patient 3 was a 36-yr-old woman with a pheochromocytoma in the middle mediastinum; it arose from the left atrium.

Patient 4 was a 27-yr-old woman with multiple endocrine neoplasia, Type 2a, who had a history of thyroidectomy for medullary thyroid carcinoma, and bilateral adrenalectomy for pheochromocytomas. There

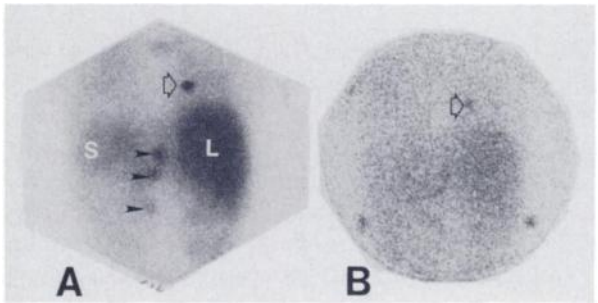


**FIG. 2.** Patient 2, posterior abdominal I-MIBG images: (A) 10 mCi I-123 MIBG imaged at 24 hr, 751 Kcounts, 20 min; (B) 0.5 mCi I-131 MIBG imaged at 24 hr, 100 Kcounts, 20 min. Arrowheads indicate residual tumor at site of previous tumor resection; open arrows metastatic lesion in rib. L = liver, S = spleen.

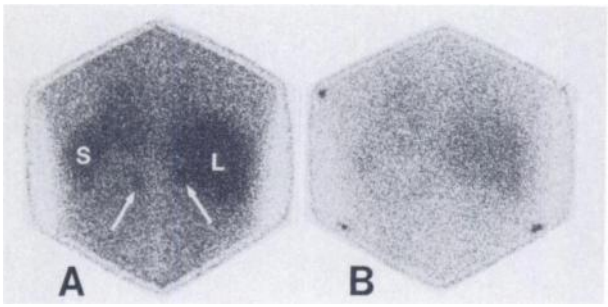


**FIG. 3.** Patient 7, posterior abdominal I-MIBG images: (A) 10 mCi I-123 MIBG imaged at 43 hr, 163 Kcounts, 12 min; (B) 0.5 mCi I-131 MIBG imaged at 48 hr, 88 Kcounts, 20 min. Arrows indicate adrenal medullae. L = liver, S = spleen.

was extensive metastatic spread of pheochromocytoma to the liver.

Patient 5 was a 10-yr-old girl with a left-sided pararenal pheochromocytoma that was barely detectable using I-131 MIBG (0.28 mCi) but clearly demonstrated using I-123 MIBG (3.9 mCi).

Patients 6 and 7 are father and daughter who each had pheochromocytomas removed from the right renal hilum. They are reported in detail elsewhere (*8*,*16*). At operation their adrenal glands were normal to palpation. Because the tumor was metastatic to lymph nodes in the daughter, and appeared grossly and histologically aggressive in the father, the patients were reevaluated. At the time of evaluation there was neither clinical nor biochemical evidence of pheochromocytoma, and neither had scintigraphic evidence of tumor. The images of Patients 6 and 7 were similar. Figure 3 shows a posterior abdominal scintigram of Patient 7 obtained with 10 mCi I-123 MIBG, which demonstrates the normal adrenal medullae.

Patient 8 was a 17-yr-old male with a 6-yr history of hypertension including more severe paroxysmal episodes. His biochemistry did not support the diagnosis of pheochromocytoma. Scintigrams obtained with I-131-MIBG and I-123 MIBG were similar to those of Patients 6 and 7.

## RESULTS

In Patients 1 to 5, who had demonstrable lesions, images of superior quality were obtained at an earlier time with 10 mCi I-123 MIBG compared with 0.5 mCi I-131 MIBG (Figs. 1 and 2). Images of similar quality were obtained in Patient 1 with 10 mCi I-123 MIBG and at 6 days following a therapeutic dose of 173 mCi I-131 MIBG (Fig. 1). Three lesions were clearly demonstrated in Patient 2 with I-123 MIBG scintigrams at 24 hr; these were not seen on diagnostic I-131 MIBG scintigrams at 24 or 48 hr (Fig. 2).

The normal adrenal glands were not visualized in any of the diagnostic I-131 MIBG scintigrams. The normal adrenal glands were clearly visible on the I-123 MIBG scintigrams in six of the eight patients imaged out to 48 hr. In Patient 4 both adrenals had been resected. In Patient 8 the adrenals were vaguely visualized, but he was imaged only out to 17 hr.

## DISCUSSION

From the MIBG scintigrams performed on patients with pheochromocytoma, it is observed that both primary and metastatic lesions may be detected successfully with both I-131 and I-123 MIBG. Image quality with a diagnostic dose (10 mCi) of I-123 MIBG was regularly superior to that obtained with diagnostic doses (0.5 mCi) of I-131 MIBG in Patients 1 to 5. In Patient 1 the definition of tumor was comparable to that with a therapeutic dose (173 mCi) of I-131 MIBG. In addition, I-123 MIBG scintigraphy has shown the ability to visualize small pheochromocytoma lesions that I-131 MIBG scintigraphy failed to demonstrate (Patient 2). The normal adrenal medullae were imaged with diagnostic doses of I-123 MIBG in six out of seven cases (the eighth case having had a bilateral adrenalectomy), and with a therapeutic dose of I-131 MIBG in Patient 1. The normal adrenal medullae were not seen in any of the diagnostic I-131 MIBG scintigrams of these eight patients. Normal adrenal medullae are seen in less than 20% of patients given diagnostic doses of I-131 MIBG, and even in these cases the definition of the glands is poor (*11*).

In comparison with I-131, I-123 is seen to have superior dosimetric characteristics, due in part to its shorter physical half-life (13 hr compared with 8 days) and freedom from $\beta$ emissions (*17*). The thyroid gland is the organ most at risk from uptake of radioiodine. The administration of stable iodide in doses of 100 mg/day may reduce this uptake to 1.0% to 0.6% (*15*), nevertheless such an uptake may lead to an appreciable radiation dose to a normal adult thyroid (20 g). The absorbed dose from a given activity of I-123 is 1/80 to 1/100 of that from I-131 (*19*).

We have observed increasing thyroidal uptake of I-131 over 6 days following the therapeutic administration of 100–200 mCi I-131 MIBG, despite the administration of iodides (*14*). This uptake is sufficient to permit visualization of the thyroid for as long as 3 wk, and represents sequestration of 0.1% to 0.2% of the administered activity liberated from the parent radiopharmaceutical by in vivo deiodination. In these patients a substantial portion of the thyroidal uptake of I-131 occurred 2 or more days after injection of I-131 MIBG, at a time when I-123 has already passed through four half-lives of physical decay. Thus it seems that the radiation to the thyroid from I-123 derived from I-123 MIBG must be proportionately less than 1/80 to 1/100 than of I-131 derived from I-131 MIBG. If less than 0.1% of I-123 enters the thyroid in the first 2 days after administration of 10 mCi of I-123 MIBG, this would deliver less than 10 $\mu$Ci of I-123 to the

**TABLE 1. COMPARISON OF ESTIMATED ABSORBED RADIATION DOSES FROM I-131 AND I-123 MIBG (rad) (MODIFIED FROM REF. *12*)**

| Organ | 0.5 mCi I-131 MIBG | 10 mCi I-123 MIBG |
|---|---|---|
| Thyroid (blocked) | 0.66* † | <0.33† |
| Adrenal medulla‡ | 50 | 8–28 |
| Heart wall‡ | 0.35 | 0.4 |
| Liver‡ | 0.2 | 0.5 |
| Spleen‡ | 0.8 | 1.5 |
| Ovary‡ | 0.5 | 0.7 |
| Total body | 0.1* | 0.2 |

* From human data.

† Thyroid dosimetry in man represents new data not presented in Ref. *12* (see text).

‡ From canine data.

**TABLE 2. RELATIVE USEFUL PHOTONS FROM I-131 AND I-123 MIBG TAKEN UP BY A PHEOCHROMOCYTOMA**

| Time after administration (hr) | Relative useful photons* 0.5 mCi I-131 MIBG | 10 mCi I-123 MIBG |
|---|---|---|
| 0 | 1 | 80.0 |
| 24 | 0.92 | 22.4 |
| 48 | 0.84 | 6.4 |
| 72 | 0.77 | 1.6 |

* Baseline reference of 0.5 mCi I-131 MIBG at 0 hr = 1.

These calculations assume that:

1. Gamma camera efficiency for I-131 = 20%.
2. Gamma camera efficiency for I-123 = 80%.
3. The number of useful photons escaping from body with I-123 is equal to that with I-131, without taking into account somewhat greater attenuation of lower-energy I-123 photons.
4. The photon yield of I-123 (84%) equals photon yield of I-131 (82%).
5. Tracer uptake is instantaneous, and retention is complete, in pheochromocytoma, and that distribution is identical for I-131 and I-123 MIBG.

thyroid, and at 13 mrad/$\mu$Ci (*18*) it would impart less than 130 mrad. To this must be added the component of the absorbed dose derived from I-123 MIBG elsewhere in the patient, which would be similar to that imparted to the whole body. Ten mCi of I-123 MIBG may be administered with radiation dosimetry similar to that of 0.5 mCi I-131 MIBG. A summary of available dosimetric data is presented in Table 1 (modified from Ref. *12*). The thyroid and whole-body data are derived from I-131 MIBG measurements in man, and the remainder from tissue distribution studies in dogs.

The 159-keV gamma emission of I-123 provides a gamma-camera efficiency approximately four times that of the 364-keV gamma of I-131. Table 2 lists the relative useful photons potentially available with 10 mCi of I-123, compared with 0.5 mCi I-131 MIBG, at various time points following administration. Currently, diagnostic studies with I-131 MIBG are performed at 24, 48, and 72 hr after administration. The high background activity in the liver and spleen generally declines more rapidly with time compared with the activity in pheochromocytomas, which retain the tracer longer (*11*). Thus, pheochromocytomas become increasingly better delineated with time. A potential disadvantage in imaging abdominal pheochromocytomas with I-123 MIBG is that its short half-life will not permit images at times when background activity will be as low as at 72 hr. Most pheochromocytomas, however, are visualized by 24 hr, and I-123 maintains a large photon flux advantage over I-131 past 48 hr (Table 2).

The potential pharmacologic effects of larger doses of I-123 MIBG arise because a 10-mCi dose of this agent (maximum 1.54 mg) contains 5.5 to 18.7 times as much MIBG as an average 0.5-mCi dose of I-131 MIBG. This does not appear to pose a threat, since the margin of safety of MIBG appears broad in animals. No observable side effects have been noted for up to 7 days following administration of 8 mg/kg MIBG to rats or 1 mg/kg to dogs, and up to 6 mg has been administered to humans (in therapy doses) without observable effects (all unpublished observations).

In conclusion, it is felt that I-123 MIBG has many advantages as an imaging agent compared with I-131 MIBG. The larger activity of I-123 MIBG that may be administered permits more accurate definition of pheochromocytomas. This is true especially for small primary and metastatic lesions. Thus, I-123 MIBG scintigraphy has the potential for a substantially lower false-negative rate than the 10% thus far associated with I-131 MIBG scintigraphy in detecting pheochromocytomas. The increased photon yield may permit emission tomographic studies with orbiting gamma cameras. Finally, the ability to visualize the normal adrenal medulla may also permit in vivo functional assessment, and provide a tool for the study of adrenal medullary physiology and pathophysiology.

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